Chemintox, Inc.
7325 Bannockburn Ridge Court
Bethesda, MD 20817
Tel. (301)-320-4506 Fax (301)-320-8258

201-15014

December 30, 2003

Mr. Michael Leavitt, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

Dear Mr. Leavitt:

On behalf of Eastman Chemical Company, I am pleased to submit the Test Plan and Robust Summaries for the substance designated as "Ketone Bottoms (KB4/KB3)" to the HPV Challenge Program, AR-201. We are submitting the test plan and accompanying robust summaries directly to EPA to make available to the public. This submission includes one electronic copy in pdf. format. A hard copy of this submission is available upon request. The EPA registration number for Eastman Chemical Company is

Please feel free to contact me with any questions or comments you might have concerning the submission at tadams@therobertsgroup.net, tadams@chemintox.com or 202-331-2325.

Sincerely,
Timothy Adams, Ph.D.
Technical Contact Person for Eastman Chemical Company

201-15014A

Test Plan for Ketone Bottoms (KB4/KB3)

Ketone Bottoms (KB4/KB3)

CAS No. 68990-20-5

Eastman Chemical Company

Registration Number

Submitted to the EPA under the High Production Volume (HPV) Challenge Program by:

Eastman Chemical Company

100 North Eastman Road

Kingsport, TN 37662

Phone: 423-229-5208

Fax: 423-224-0208

Table of Contents

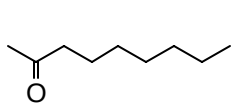
The HPV Challenge Program

Test Plan for Ketone Bottoms (KB4/KB3)

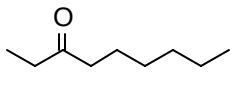
1 IDENTITY OF SUBSTANCES

Ketone Bottoms 4 (KB4)

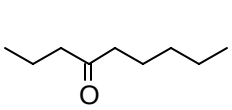
Nonanone isomers and structurally related isomers (17.2%)



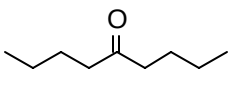
2-nonanone
CAS No. 821-55-6



3-nonanone
CAS No. 925-78-0

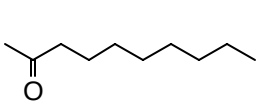


4-nonanone
CAS No. 4485-09-0

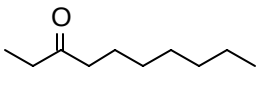


5-nonanone
CAS No. 502-56-7

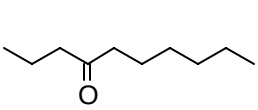
Decanone isomers and structurally related isomers (13.3%)



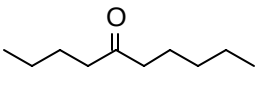
2-decanone
CAS No. 693-54-9



3-decanone
CAS No. 928-80-3

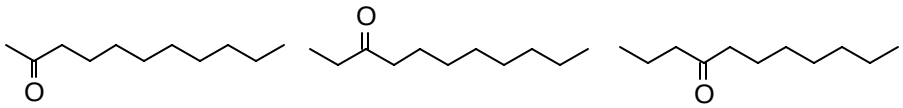


4-decanone
CAS No. 624-16-8



5-decanone
CAS No. 820-29-1

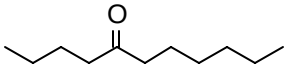
Undecanone isomers and structurally related isomers (17.8%)



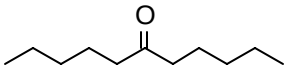
2-undecanone
CAS No. 112-12-9

3-undecanone
CAS No. 2216-87-7

4-undecanone
CAS No. 14476-37-0

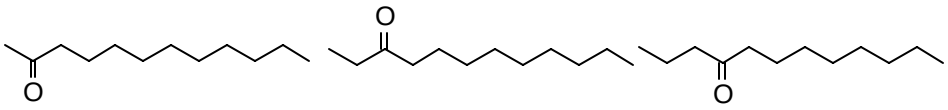


5-undecanone
CAS No. 33083-83-9



6-undecanone
CAS No. 927-49-1

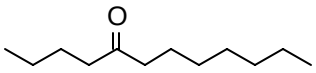
Dodecanone isomers and structurally related isomers (3.4%)



2-dodecanone
CAS No. 6175-49-1

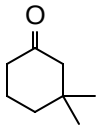
3-dodecanone
CAS No. 1534-27-6

4-dodecanone
CAS No. 6137-26-4



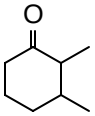
5-dodecanone
CAS No. 19780-10-0

Dimethylcyclohexanone isomers (10.8%)



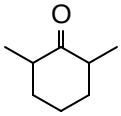
3,3-dimethylcyclo hexanone

CAS No.2979-19-3



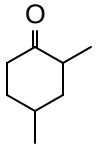
2,3-dimethylcyclo hexanone

CAS No.13395-76-1



2,6-dimethylcyclo hexanone

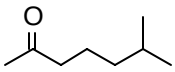
CAS No.2816-57-1



2,4-dimethylcyclo hexanone

CAS No.823-55-2

6-Methyl -2-heptanone (2.5%)

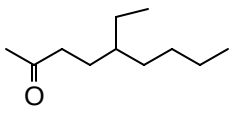


6-methyl-2-heptanone

CAS No.928-68-7

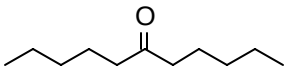
Ketone Bottoms 3 (KB3)

Undecanone isomers (approximately 35%)



5-ethyl-2-nonanone
CAS No. 5440-89-1
17.7%

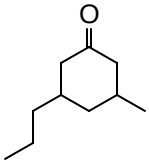
+



6-undecanone
CAS No. 927-49-1
14.2%

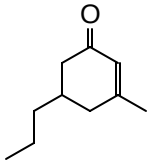
+ other C_{11} ketones
(*e.g.*, 3-butyl-2-heptanone)

Cyclohexanone/cyclohexyl derivatives (approximately 16%)



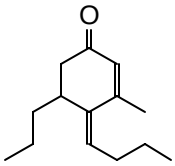
3-methyl-5-propyl
cyclohexanone
CAS No. 67662-89-0
4.5%

+



3-methyl-5-propyl
cyclohexenone
3.1%

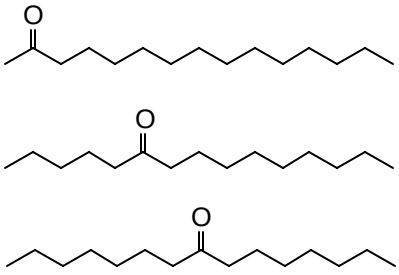
+



3-methyl-4-butylidene-
5-propyl-2-cyclohexenone
3.4%

+ other cyclohexyl
derivatives
5.3%

Mixture of 2-pentadecanone (CAS No. 2345-28-0), 6-pentadecanone (CAS No. 1001-45-2), and 8-pentadecanone (CAS NO. 818-23-5) (approximately 5%)



2 CATEGORY ANALYSIS

2.1 Introduction

In November of 1999, Eastman Chemical Company (Eastman) committed to participate in the Chemical "Right-to-Know" Program. As part of this commitment, Eastman is committed to assembling and reviewing available test data, developing and providing a test plan for the ketone mixtures recognized as Ketone Bottoms 4 and Ketone Bottoms 3 (KB4 and KB3), and, where needed, conducting additional testing. The CAS No. for KB4 and KB3 is 68990-20-5. The test plan and robust summaries presented are the first phase of Eastman's commitment to the Chemical "Right-to-Know" Program.

2.2 Background Information

The chemical category designated "Ketone Bottoms 4 (KB4)" consists of a continually varying mixture of linear- and branched-chain aliphatic ketones possessing carbon chain lengths from C_9 to C_{12}. These ketones account for approximately 50% of the mixture. The remaining constituents of known structures in KB4 include a mixture of dimethylcyclohexanones (10.8%) and 6-methyl-2-heptanone (2.5%). Based on the boiling point range for the distillate KB4 and the method of production, it is anticipated that the portion of KB4 of unknown composition is a complex mixture of ketones of similar molecular weight and structure. Similar to KB4, "Ketone Bottoms 3 (KB3)" is a mixture of linear- and branched-chain aliphatic and alkyl-substituted cyclohexanone derivates ketones. Isomers of undecanone constitute more than 35% of KB3 with smaller amounts of cyclohexanone (11%) and pentadecanone derivatives (5%). Other ketones in KB3 contain from 9 to 15 carbons.

Many of the constituents of KB4 and KB3 are common components of traditional foods occurring in fruits, cheese, meats, and some vegetables [CIVO-TNO, 1999]. 2-Nonanone, 3-nonanone, 2-undecanone, 2-tridecanone, 2-pentadecanone, a variety of isomeric branched-chain ketones and methyl-substituted cyclohexanones are currently recognized

by the U.S. Food and Drug Administration (FDA) as GRAS ("generally regarded as safe") for their intended use as flavoring substances [Hall and Oser, 1965]. These ketones have also been evaluated by The Joint Expert Committee on Food Additives (JECFA) as part of the World Health Organization (WHO). JECFA has reviewed numerous constituents of the KB4 and KB3 mixtures and approved them for use in flavors at current levels of intake [JECFA, 1999, 2003]. Quantitative natural occurrence data indicate that oral intake of these substances occurs predominantly from consumption of food in which they occur naturally [Stofberg and Grundschober, 1987; Stofberg and Kirschman, 1985]. Based on the long term recognition of many of these ketones as GRAS in the United States, their recognition as safe for addition to food by JECFA, and their widespread natural occurrence in food, it is recommended that no additional studies are required to meet human health endpoints in the High Production Volume (HPV) Chemical "Right to Know" Program.

2.3 Structural Classification

The chemicals of known structure in the KB4 and KB3 mixtures exhibit common skeletal and functional group features. Aliphatic linear and branched-chain substances in KB4 and KB3 are homologues with chain length from 9 to 15 carbons. Other constituents of the mixture are alkyl-substituted cyclohexanones or simple branched-chain aliphatic ketones. All contain a single ketone functional group. The stereochemistry of the alkyl-substituted cyclohexanones is not defined. Therefore all possible *cis* and *trans* isomers are anticipated. Primarily, KB4 and KB3 are composed of a mixture of higher molecular weight (greater than C_9) saturated aliphatic ketones and alkyl-substituted cyclohexanones.

2.4 Industrial Production

Eastman Chemical Company produces two products (KB4 and KB3) that originate as by-products from the manufacture of low molecular weight (C_6-C_7) straight-chain and branched aliphatic ketones and during the production of a C_5 straight-chain aliphatic ketone. These products are a high-boiling fraction removed from the primary products by

distillation as an underflow stream and are commonly referred to as "ketone bottoms" (KB3 and KB4). The distillation process is controlled so as to limit the concentration of low-boiling components in this stream. In addition, all manufacturing processes are considered as closed processes. The material is piped to on-site storage tanks and is than transported by tanker truck or railcar to other industrial locations.

2.5 Chemical Reactivity and Metabolism

2.5.1 Aliphatic Linear Ketones

Aliphatic ketones in this group are rapidly absorbed through the gastrointestinal tract and eliminated from the blood. Peak blood levels are normally obtained within 1-2 hours after dosing [Lehman *et al.*, 1945; Nordmann *et al.*, 1973; Bonte *et al.*, 1981]. The corresponding secondary alcohols (*i.e.*, 2-nonanol is the corresponding secondary alcohol of 2-nonanone) are also rapidly absorbed and readily converted to the corresponding ketone *in vivo*. Although ketones and secondary alcohols are readily interconverted in animals, reduction of the ketones by cytosolic carbonyl reductases [Felsted and Bachur, 1980] is favored yielding the corresponding secondary alcohols that are rapidly excreted in the urine mainly as glucuronic acid conjugates [Kasper and Henton, 1982; Gry, 1999].

In the case of a methyl ketone, the terminal methyl group may undergo oxidation, eventually yielding *alpha*-ketoacid that is the substrate for further cleavage and oxidation in the fatty acid pathway and citric acid cycle [Wouters and Speijers, 1999]. Therefore, a substance such as 2-nonanone is anticipated to be either reduced to 2-nonanol and excreted as the glucuronic acid conjugate or undergo *alpha*-oxidation and cleavage to eventually yield shorter chain acids that enter the fatty acid pathway and are eventually completely metabolized to carbon dioxide and water.

A third metabolic option, which for higher molecular weight (MW) ketones is a minor pathway, is *omega*- and/or *omega*-1-oxidation. Although for most ketones, this oxidation yields polar metabolites that are further oxidized and/or excreted, exposure to high levels of ketones that undergo *omega*- and/or *omega*-1-oxidation to form *gamma*-diketones (*e.g.*

2,5-hexadione) are known to exhibit a neurotoxic phenomenon known as "giant axonal swelling". This toxicity is observed at high levels of exposure and is limited to ketones that have structural features (2-hexanone, 3-heptanone, and 5-nonanone) that permit primarily *omega*-1-oxidation to yield a *gamma*-diketone. Of ketones with chain length equal to or greater than six, the effect is most pronounced for 2-hexanone. Higher MW ketones such as 3-heptanone and 5-nonanone only exhibit this effect at or near the lethal dose levels. However, because this is an intoxication pathway, it will be discussed in detail with emphasis on its relationship to the only ketone in KB4 that could possibly show this phenomenon, 5-nonanone.

2.5.1.1 Reduction of Aliphatic Linear Ketones

In studies limited to the identification of urinary glucuronide metabolites, relatively high single dose levels of a homologous series of aliphatic secondary alcohols and ketones were administered individually by gavage to rabbits. The urinary excretion of glucuronic acid conjugates was determined after 24 hours [Kamil *et al.*, 1953]. The substances, dose levels, and average urinary output of glucuronide (%) are listed in Table 1. The results demonstrate that secondary alcohols, either administered directly or formed *via* ketone reduction, are largely excreted as glucuronic acid conjugates.

TABLE 1 - ALIPHATIC SECONDARY ALCOHOLS AND KETONES ADMINISTERED TO RABBITS VIA GAVAGE

Substance	Dose, mg/kg bw[1]	% Urinary glucuronic acid conjugate
2-pentanol	735	44.8
2-heptanone	950	41.0
2-heptanol	965	54.6
3-heptanol	965	61.9
2-octanol	1081	15.5

[1] Calculated based on dose of 25 mmole/3 kg of rabbit

2.5.1.2 omega-Oxidation of Methylketones

Aliphatic secondary ketones that are also methyl ketones have additional metabolic options available for the detoxication and excretion of these substances. Methyl ketones

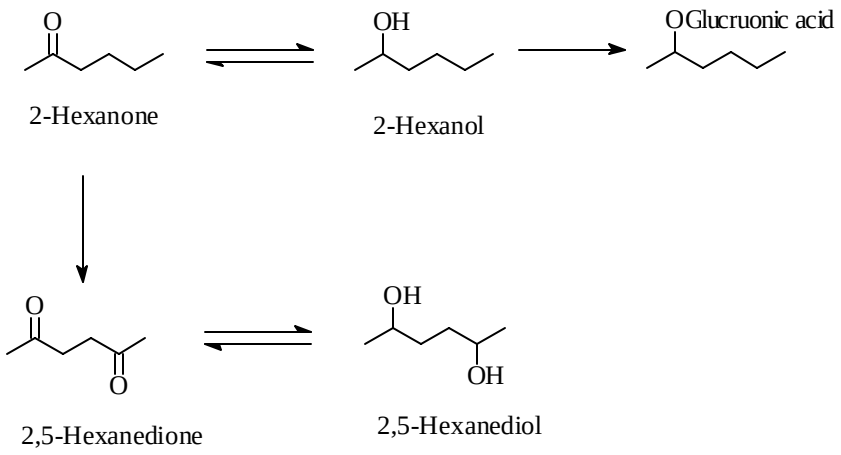
undergo *alpha*-hydroxylation and subsequent oxidation of the terminal methyl group to yield corresponding ketocarboxylic acids [Gabriel *et al.*, 1972]. The ketoacids are intermediary metabolites (*e.g. alpha*-ketoacids) that undergo oxidative decarboxylation to yield carbon dioxide and simple aliphatic carboxylic acids. The acids may be completely metabolized in the fatty acid pathway and citric acid cycle. The metabolism of *alpha*-hydroxyacids and *alpha*-ketoacids was recently reviewed [Abbott, 2000].

2.5.1.3 omega- and/or omega-1-Oxidation

Even though longer-chain aliphatic ketones (*i.e.*, carbon chain length $\geq C_5$) are primarily metabolized *via* reduction, *omega*- and/or *omega*-1-oxidation are competing pathways at high concentrations (see Figure 1). In a metabolic study, guinea pigs were given a single intraperitoneal injection of, either 450 mg 2-butanone, 2-hexanone[1] or 5-methyl-2-hexanone[1]/kg bw in corn oil (25%). Blood serum was collected at 1, 2, 4, 6, 8, and 16 hours. Identified metabolites were then administered separately to animals at the same dose level. Analysis of blood serum revealed metabolites formed *via* ketone reduction and *omega*-1-oxidation. 2-Hexanone (2H) was metabolized by reduction to yield 2-hexanol (2OH), and *omega*-1 oxidation to yield 5-hydroxy-2-hexanone (5H2H), and then 2,5-hexanedione (25HD). The respective serum half-lives and clearance times of 5H2H (156 minutes and 8 hours) and 25HD (100 minutes and 16 hours) were approximately twice that of the parent ketone 2H (78 minutes and 6 hours) or the 2OH metabolite (72 minutes and 6 hours). When 2OH was administered to guinea pigs at the same dose level, the parent ketone 2H and *omega*-1-oxidation metabolites (5H2H, 25HD, and 2,5-hexnaediol) were identified in the serum. Intraperitoneal administration of *omega*-1-oxidation metabolites 2H5H and 25HD demonstrated that *omega*-1-oxidation metabolites were inconvertible in serum [Dietz *et al.*, 1981].

[1] A structurally related substance that is not a flavoring substance.

FIGURE 1. *OMEGA*-1-OXIDATION OF ALIPHATIC KETONES



In guinea pigs administered 5-methyl-2-hexanone, the metabolites of ketone reduction (5-methyl-2-hexanol, respectively) and *omega*-1-oxidation (5-hydroxy-5-methyl-2-hexanone, respectively) were the major serum metabolites. No diketone was detected [Dietz *et al.*, 1981]. 2-Butanone and 4-methyl-2-hexanone have been detected in the serum, urine and expired air of healthy adults [Conkle *et al.*, 1975; Zlatkis *et al.*, 1980]. A recent review of aliphatic ketones [Topping *et al.*, 1994] contains a comprehensive discussion of the human pharmacokinetics and metabolism of 2-butanone.

Higher homologues also metabolize *via* carbonyl reduction and *omega*-1-oxidation. In rats, 2-heptanone (No. 8) was metabolized to 2-heptanol (No. 9) and 2,6-heptanedione, the not being a *gamma*-diketone does not exhibit neurotoxicity [Topping *et al.*, 1994].

At high dose levels, *omega*- and/or *omega*-1-oxidation of certain aliphatic ketones may yield *gamma*-diketones. 3-Heptanone may yield 2,5-hexanedione and 2,5-heptanedione while 5-nonanone may yield 2,5-nonanedione. At high levels of exposure, these diketone

metabolites exhibit a peripheral neuropathy commonly recognized as "giant" axonal neuropathy [Krasavage *et al.*, 1980]. The structural features of diketone metabolites required to induce peripheral neuropathy have been well characterized. The position of the ketone functions on the aliphatic chain must be 2,5- (*i.e., gamma*). *gamma*-Diketones with terminal methyl substituents (*e.g.*, 2,5-hexanedione) and/or methyl substituents at the 3 and 4 positions exhibit the most pronounced effect. The intensity of the peripheral neuropathy depends on the size and position of alkyl substituents on the *gamma*-diketone. For example, the strongest neurotoxic effects have been observed for 3,4-dimethyl substituted 2,5-hexanedione (not a flavoring substance). When the methyl substituents are removed and the chain length is increased (*i.e.*, C_7 and greater) the neurotoxic response is significantly mitigated [Topping *et al*., 1994].

5-Nonanone is the only ketone in the KB4 mixture containing structural features that permit a neurotoxic *gamma*-diketone to form [O'Donoghue *et al.*, 1982]. In a study of commercial-grade 5-methyl-2-octanone (72.29%) containing 5-nonanone (11.63%) as an impurity, rats were given 2000 mg/kg bw of the mixture orally by gavage for 90 days. After 59 days, clinical signs of neurotoxicity (tail droop and extension of hind-limb) were observed. The treatment of rats with 2000 mg/kg bw/day of pure 5-nonanone produced signs of peripheral neuropathy. Serum analysis showed the presence of 2,5-nonanedione and the neurotoxic agent, 2,5-hexandione, presumably formed as a secondary metabolite after oxidation and chain cleavage reactions. Animals given 233 mg/kg bw of 5-nonanone for 90 days showed no signs of general or neurological toxicity. In conclusion, the presence of a butyl side-chain mitigates the neurotoxic effect of 5-nonanone, which is observed only at extremely high dose levels (greater than 2000 mg/kg bw oral dose levels).

In a study investigating the neurotoxic effects of other aliphatic ketones, 3-heptanone administered to female Wistar rats *via* drinking water at 1000 mg/kg bw/day for 120 days did not produce any evidence of neurotoxicity [Homan and Maronpot, 1978]. Male Crl rats (3/group) were exposed to atmospheres containing 700 ppm 3-heptanone for 2-20 hour and 2-16 hour periods per week. Animals were subjected to 88 exposures over 164 days (approx. 24 weeks). After the 4^{th}, 30^{th}, and 85^{th} exposure, blood serum was analyzed

for 2,5-heptanedione. Maximum mean serum levels reached 10 micrograms 2,5-heptanedione/ml after 4 exposures but decreased to 6-7 micrograms 2,5-heptanedione/ml after 30 and 85 exposures. No neurotoxicity was observed [Katz *et al.*, 1980]. In a gavage study, Crl rats (2/group) were given 250, 500, 1000, 2000, or 4000 mg/kg bw of 3-heptanone (No. 10) for 5 days per week for 14 weeks. Total 48 hour urinary excretion of *gamma*-diketone (*i.e.*, 2,5-hexanedione and 2-5-heptanedione) was measured during the last week of the study and was 1.28 or 2.14 mg, respectively, for animals administered 1,000 or 2,000 mg/kg bw of 3-heptanone. No peripheral neuropathy was observed after 14 weeks at any dose level up to and including 1000 mg/kg bw. At a dose (2000 mg/kg bw) approaching the LD50 (2760 mg/kg) in rats, 3-heptanone did induce peripheral neuropathy [O'Donoghue *et al.*, 1984].

2.5.2 Summary of Metabolism and Excretion for Aliphatic Ketones

Data demonstrate that the reviewed group of secondary alcohols and aliphatic ketones undergo efficient metabolic detoxication. Metabolism of aliphatic ketones occurs primarily *via* reduction to the corresponding secondary alcohol. Secondary alcohols are metabolized by conjugation with glucuronic acid followed by excretion primarily in the urine. Short-chain aliphatic ketones may also be metabolized *via omega*- and/or *omega*-1-oxidation, and/or they may be excreted unchanged in expired air. *omega*-Oxidation and/or *omega*-1-oxidation become competing pathways for longer-chain aliphatic ketones at high concentrations. The only identified intoxication pathway (*i.e.*, formation of a neurotoxic *gamma*-diketone) applies strictly to 5-nonanone. However, the threshold for activation of this intoxication pathway occurs at near-lethal dose levels.

2.5.3 Alkyl-substituted cyclohexanones

Cyclohexanone and alkyl-substituted cyclohexanones are rapidly absorbed through the gastrointestinal tract and rapidly eliminated from the blood. Peak blood levels are normally reached within 1-2 hours after dosing. The cyclohexanone derivative may be reduced to cyclohexanol by cytosolic carbonyl reductases. Conversely, unsubstituted or

alkyl-substituted cyclohexanol is rapidly oxidized *in vivo* to the corresponding cyclohexanone derivative by alcohol dehydrogenase. Hence, just as for aliphatic ketones, cyclohexanone and cyclohexanol derivatives are inconvertible *in vivo.* Conjugation of the alcohol with glucuronic acid and excretion in the bile and urine provides the predominant pathway for metabolic detoxication and elimination of both cyclohexanol and cyclohexanone derivatives.

Male Sprague-Dawley rats were exposed to atmospheres of either 400 ppm (240 mg/kg bw) or 1,600 ppm (980 mg/kg bw) cyclohexanone for 6 hours. Twenty-four hour post-exposure, terminal blood and urine samples show the average plasma levels of cyclohexanone and cyclohexanol for the 400 ppm and 1,600 ppm exposures were 26 and 20 micrograms/ml and 122 and 140 micrograms/ml, respectively. The total urinary excretion of cyclohexanol was at least 10 times that of cyclohexanone (16 and 15 micrograms and 143 and 264 micrograms at the 400 and 1600 ppm exposures, respectively) with 13 micrograms and 72 micrograms of conjugated cyclohexanol being excreted within 72 hours at 400 ppm and 1,600 ppm, respectively [Topping *et al*., 1994].

In another study, four rabbits were each given cyclohexanone (No. 1100) in water by gavage. Urine collected at 18 hours after dosing revealed 66% of the 248 mg/kg oral dose was excreted as the glucuronic acid conjugate of cyclohexanol [Elliott *et al.*, 1959]. The authors concluded that cyclohexanone is first reduced to cyclohexanol and then conjugated with glucuronic acid prior to excretion in the urine.

Male beagle dogs were given 284 mg/kg bw of cyclohexanone by intravenous injection daily. Cyclohexanol was detected in the plasma within 30 minutes of injection. The mean distribution and elimination half-lives of cyclohexanone and cyclohexanol are 6.6 and 81 minutes, respectively. The mean steady state volume of distribution for cyclohexanone is 2.6 L/kg and the mean total body clearance for cyclohexanone is 27.4 ml/kg/minutes. [Martis *et al.*, 1980; Koeferl *et al.*, 1981]. When 328 mg/kg bw cyclohexanol was administered by intravenous injection, it showed a plasma half-life of 99 minutes, an apparent distribution volume of 1.2 L/kg and a total body clearance of 8.8 ml/kg/minutes. Based on these data cyclohexanone and cyclohexanol are rapidly cleared from the body

[Martis *et al.*, 1980]. Approximately 60% of cyclohexanone administered was recovered in the urine as a glucuronide conjugate of cyclohexanol after 24 hours. The direct renal clearance of unmodified cyclohexanone and cyclohexanol is a minor route of elimination accounting for less than 1% of administered dose. It is proposed that 74-100% of cyclohexanone is converted to cyclohexanol and further metabolized before elimination. The authors propose that some of the cyclohexanone may be expelled through the lungs [Martis *et al.*, 1980; Koeferl *et al.*, 1981].

Four men and four women volunteers were exposed to an environment containing atmospheric concentration of 101, 207, or 406 mg/cu.m of cyclohexanone for 8 hours. Urine collected at 2-hour intervals during exposure, and for 72 hours post-exposure, shows the presence of glucuronic acid conjugates of cyclohexanediol with peak excretion rate at about 16 hours post-exposure. Approximately 60% of the cyclohexanone dose is excreted within the 72-hour period [Mraz *et al.*, 1994].

An adult man ingested 100 ml of liquid adhesive containing 39% cyclohexanone. The cyclohexanone was rapidly absorbed. Plasma and urine levels of cyclohexanone and metabolites were unaffected by gastric lavage (5.5 L saline), two plasma exchanges (2.4 L each) and hemoperfusion when compared to pre-treatment values. Cyclohexanol and cyclohexanone were detected in the plasma for up to 25 hours post ingestion. Cyclohexanone levels were at the lower limit of detection; however, plasma levels of cyclohexanol were high, 220 micrograms/ml 5 hours after ingestion and decreased to 10 micrograms/ml after 20 hours. High levels of cyclohexanol glucuronide were detected in the urine for up to 48 hours. Urinary excretion of the parent ketone was described as minimal. The elimination half-life of cyclohexanone in human plasma was determined at 4.75 hours and the rate of elimination (K_e) 0.145 micrograms/ml/hour. This indicates that the mechanism of elimination in humans involves conversion of the cyclohexanone to cyclohexanol followed by conjugation with glucuronic acid [Sakata *et al.*, 1989].

Other unsubstituted alicyclic ketones (*e.g.*, cyclopentanone) are rapidly absorbed, metabolized, conjugated and excreted mainly in the urine [James and Waring, 1971]. The urine collected from rabbits orally administered 193 mg/kg bw cyclopentanone was taken

and treated with *beta*-glucuronidase. The resulting analysis revealed that the major urinary component was a glucuronic acid conjugate of cyclopentanol [James and Waring, 1971].

The size, position, number, or stereochemistry of alkyl substituents on the cyclohexyl ring exerts no significant effect on the rate of absorption, metabolism and excretion of alkyl-substituted cyclohexanol or cyclohexanone derivatives. Alkyl-substituted cyclohexanones are also rapidly absorbed, reduced to the corresponding cyclohexanol derivatives that are then conjugated with glucuronic acid and also excreted mainly in the urine. Alkyl-substituted cyclohexanols are rapidly absorbed, conjugated with glucuronic acid, and excreted mainly in the urine.

The urine of groups (6 to 10) of doe albino rabbits was pooled 24 hours after each animal received a single oral dose of 652 mg/kg bw of (±)-2-*tert*-butylcyclohexanone, 652 mg/kg bw of (±)-3-*tert*-butylcyclohexanone, or 562 mg/kg bw of 4-*tert*-butylcyclohexanone [Cheo *et al*., 1967]. The mean % of the dose excreted as the glucuronic acid is 76.5, 90, or 80% respectively.

Rabbits given oral doses of 1,750 mg/kg bw of methylcyclohexanol (mixture of isomers) or 560 mg/kg bw of methylcyclohexanone (mixture of isomers) predominantly excrete the glucuronic acid of methylcyclohexanol within the first 24 hours [Treon *et al*., 1943a]. Rabbits were exposed to atmospheres containing 2.3 (503 ppm), 1.06 (232 ppm), or 0.56 mg/L (121 ppm) of methylcyclohexanol (mixture of isomers), 6 hours daily, 5 days per week for 10 weeks. Mean daily urinary output of glucuronic acid conjugates during exposure is proportional to dose. Rabbits exposed to atmospheres containing 2.31 (514 ppm) or 0.816 mg/L (132 ppm) of methylcyclohexanone (mixture of isomers), 6 hours daily, 5 days per week for 10 weeks exhibit mean daily urinary output of glucuronic acid proportional to dose [Treon *et al.*, 1943b].

Rats received 500 mg/kg bw (128 microcurie/mg) of 3-^{3}H-2-isopropyl-5-methylcyclohexanol and urine and feces were collected 24 and 48 hours after dosing. The total excretion of 3-^{3}H-2-isopropyl-5-methylcyclohexanol by intact and bile duct-cannulated rats was greater than 70% of the dose at 48 hours. The glucuronic acid

conjugate of 2-isopropyl-5-methylcyclohexanol and other minor oxidized metabolites are present in urine and fecal extracts. The glucuronic acid conjugate is also the main metabolite in the bile, while the glucuronic acid conjugate and minor metabolites (less than 5%) formed by side-chain oxidation are excreted in the urine [Yamaguchi *et al.*, 1994].

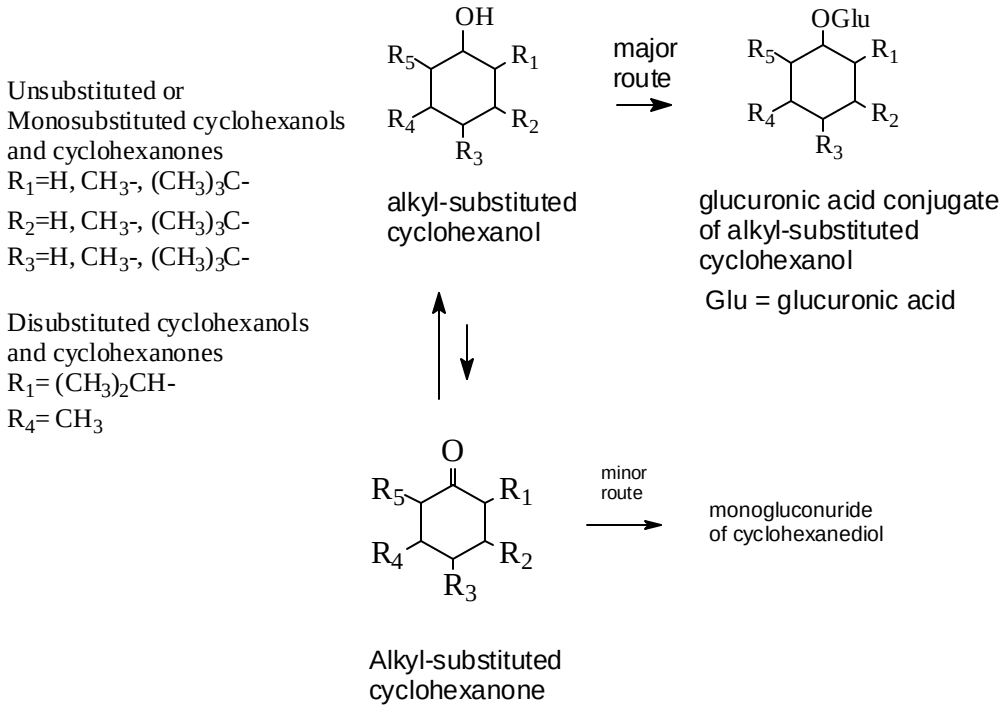
2.5.4 Summary of Metabolism

In summary, alkyl-substituted cyclohexanones are interconvertible with their corresponding alcohols *in vivo.* In the principal excretion pathway, the cyclohexanols are conjugated with glucuronic acid and excreted primarily in the urine.

As indicated above, the major metabolic pathway involves reduction of the cyclohexyl ketones to yield the corresponding cyclohexanols that are subsequently excreted primarily as the glucuronic acid conjugates [Lington and Bevan, 1994; Topping *et al.*, 1994; Cheo *et al.*, 1967; Elliott *et al.*, 1965; Yamaguchi *et al.*, 1994]. To a very minor extent, alicyclic ketones and secondary alcohols containing an alkyl side-chain undergo oxidation of the side-chain to form polar poly-oxygenated metabolites that are also excreted as the glucuronide or sulfate conjugates mainly in the urine.

Although it has been anticipated that more lipophilic ketones or ketones with sterically hindered functional groups would undergo more extensive oxidation of alkyl ring substituents [Nelson *et al.*, 1992], studies with 2-, 3-, or 4-methylcyclohexanone, 2-isopropyl-5-methylcyclohexanol, 3,5,5-trimethylcyclohexanol, and even 2-, 3-, or 4-*tert*-butyl-substituted cyclohexanone or cyclohexanols reveal that conjugation of the cyclohexanol moiety by glucuronic acid is the predominant excretion pathway regardless of the size or position of the ring substituent. In general, the metabolic fate of alkyl-substituted cyclohexanone and cyclohexanol derivatives is similar to that of the un-substituted homologues (see Figure 2) [Lington and Bevan, 1994; Topping *et al.*, 1994].

FIGURE 2 - METABOLIC FATE OF CYCLOHEXYL DERIVATIVES IN ANIMALS



In rats and rabbits, 66% of a 186 mg/kg bw dose of cyclohexanone or 47% of a 193 mg/kg bw dose of cyclopentanone *via* gavage is reduced to the corresponding secondary alcohol and excreted in the urine as the glucuronic acid conjugate [James and Waring, 1971]. Also, detected are trace amounts of mercapturic acid conjugate of the 2-hydroxycyclohexyl derivative [James and Waring, 1971]. Eighteen (18)-hour urine samples from rabbits administered 1,500 mg of cyclohexanone by gavage contain 65% cyclohexanol and a minor amount (6%) of *trans*-cyclohexane-1,2-diol as monoglucuronide conjugates [Elliott *et al.*, 1959]. Presumably, the diol forms by hydroxylation at the *alpha*-position of cyclohexanone followed by reduction of ketone function. The corresponding cyclohexanol derivative is the major urinary metabolite obtained from rabbits fed 460 mg/kg bw cyclohexane, 260 mg/kg bw cyclohexanol, or 350 mg/kg bw cyclohex-1-en-1-yl acetate [Elliott *et al.*, 1959].

The urine of rabbits given an oral dose of 1,200 mg/kg bw of cyclohexanol, shows a significant increase in glucuronic acid conjugates and decrease in inorganic sulfate compared to pre-dose levels [Treon *et al.*, 1943a]. The glucuronic acid conjugate of cyclohexanol is also obtained as the major urinary metabolite in rabbits given 890 mg/kg bw of cyclohexanone [Treon *et al*., 1943a]. The glucuronic acid conjugate of cyclohexanol (1.55 mg/L) and small amounts of cyclohexanone (0.23 mg/L) were found in the urine of workers occupationally exposed to a mixture of atmospheric hexanes including 456 mg/cu.m of cyclohexane [Governa *et al.*, 1987; Perbellini *et al.*, 1980]. The authors concluded that the cyclohexane is transformed to cyclohexanol that subsequently form glucuronic acid and sulfate conjugates.

Rats and rabbits were given oral doses of 200 - 3200 mg/kg bw of 2-, 3-, or 4-methylcyclohexanone. The glucuronic acid and sulfate conjugates of the corresponding secondary alcohols were the predominant urinary metabolites [Treon *et al.*, 1943a; Elliott *et al.*, 1959; Tao and Elliott, 1962].

Although the glucuronic acid conjugation of the alcohol is the predominant excretion pathway, oxidation of the alkyl substituents to yield poly-oxygenated metabolites has been reported as a minor pathway in animals. The number of possible polyoxygenated metabolites increases with an increase in the types of alkyl ring substituents (*e.g.*, methyl and isopropyl substituents) [Nelson *et al*., 1992; Yamaguchi *et al*., 1994; Madyastha and Srivatsan, 1988; Asakawa *et al*., 1986].

The glucuronic acid conjugate of 2-, 3-, or 4-*tert*-butylcyclohexanol is the major urinary metabolite obtained 24 hours after rabbits were given 652 mg/kg bw of (±)-2-*tert*-butylcyclohexanone, 652 mg/kg bw of (±)-3-*tert*-butylcyclohexanone, or 562 mg/kg bw of 4-*tert*-butylcyclohexanone, respectively [Cheo *et al.*, 1967]. The mean percent of dose excreted is 76.5, 90, or 80% for 2-, 3-, or 4-*tert*-butylcyclohexanone, respectively. The ratio of *cis*- to *trans*-*tert*-butylcyclohexanol present in the urine of animals given 2-(71:29), 3-(74:26), or 4(26:74)-*tert*-butylcyclohexanone provides evidence that carbonyl reductase catalyzed reduction of the ketone function with NADH is influenced by steric effects of the *tert*-butyl substituent. The authors suggest that NADH uses a perpendicular

approach to the carbonyl function in 2- and 3-*tert*-butylcyclohexanone. The 4-*tert*-butyl substituent, being more removed from the reaction cite, exerts only a minor impact on stereochemistry of the reduction of the ketone to the alcohol. In contrast, a "face to face" approach is used during the reduction of the corresponding smaller alkyl substituents (*e.g.*, methyl-substituted cyclohexanones) by NADH. In these cases, the *trans* isomer is favored [Elliott *et al.,* 1965].

The presence of multiple alkyl substituents at different positions on the cyclohexyl ring does not significantly alter the principal pathway of metabolism and excretion. 2-Isopropyl-5-methylcyclohexanone and the corresponding alcohol are mainly conjugated with glucuronic acid. At higher dose levels, *omega*-oxidation of the side chain substituents occurs to yield various polyols and hydroxyacids of 2-isopropyl-5-methylcyclohexanol [Yamaguchi *et al*., 1994; Madyastha and Srivatsan, 1988]. The unchanged alcohol and minor metabolites formed by side chain oxidation are eliminated in the urine and feces either unchanged or conjugated with glucuronic acid [Yamaguchi *et al*., 1994]. 2-Isopropyl-5-methylcyclohexanone is primarily reduced to the corresponding secondary alcohol that is then eliminated as noted above [Williams, 1940].

The metabolic fate of 2-isopropyl-5-methylcyclohexanol and 2-isopropyl-5-methylcyclohexanone has been studied in humans and other animals. Seventy-nine percent (79%) of a 1,000 mg oral dose [Quick, 1928] or 78% of a 10-20 mg oral dose [Atzl *et al.*, 1972] of 2-isopropyl-5-methylcyclohexanol administered to volunteers is eliminated as the glucuronic acid conjugate. For eight days, 750 mg of the *l* stereoisomer of 2-isopropyl-5-methylcyclohexanol was orally administered to three human volunteers followed by oral or intravenous administration of 200 mg [6-^{13}C]-glucuronolactone or [6-^{13}C]-sodium glucuronate. For two days after the administration of the isotopic compound, the glucuronic acid conjugate of 2-isopropyl-5-methylcyclohexanol is excreted in daily yields up to 84% of the 2-isopropyl-5-methylcyclohexanol administered [Eisenberg *et al.*, 1955]. In two separate studies involving a total of 19 male and female volunteers, the glucuronic acid conjugate of 2-isopropyl-5-methylcyclohexanol is detected in the urine following oral administration of a 180 mg dose of an essential oil (peppermint oil) containing greater than 80% of 2-isopropyl-5-methylcyclohexanol, its stereoisomers, and

the corresponding ketone [Kaffenberger and Doyle, 1990]. A 4,500 mg/kg bw oral dose of 2-isopropyl-5-methylcyclohexanol administered to rabbits is conjugated with glucuronic acid and eliminated in the urine [Deichmann and Thomas, 1943; Williams, 1939; Quick, 1924].

In rats, the vast majority of orally administered 2-isopropyl-5-methylcyclohexanol is eliminated in either the urine or feces as the glucuronic acid conjugate or, to a lesser extent, as various oxidation products of the alcohol [Yamaguchi *et al*., 1994; Madyastha and Srivatsan, 1988]. Non-cannulated and bile duct-cannulated male Fischer 344 rats (5/sex) were administered a single dose of 500 mg/kg bw of [3-^{3}H]-*l*-2-isopropyl-5-methylcyclohexanol. Urine and feces were collected over the next 24 and 48 hours in non-cannulated rats. In the bile duct-cannulated rats, bile samples were collected in two-hour intervals for the first six hours (3 collections) and then from 6-24 hours. Urine was collected at 24 hours.

In the non-cannulated rats, total recovery of the labeled substance in the urine or feces is 71.7% with the majority of the dose (45.4%) being recovered within the first 24 hours. In the urine, 37.8% percent of the radioactivity is excreted with equal amounts for the first and second 24 hours. In the feces, 33.9% of the radioactivity is recovered with the majority in the first 24 hours (26.6%) [Yamaguchi *et al.*, 1994]. In the bile duct-cannulated rats, total recovery of the labeled substance in the urine or bile is 74.2% with the majority being recovered in the bile (66.9%). The bile metabolites are the mainly glucuronic acid conjugate of 2-isopropyl-5-methylcyclohexanol along with a variety of oxidation products in which the alkyl substituents (isopropyl or methyl substituents) of 2-isopropyl-5-methylcyclohexanol are oxidized [Yamaguchi *et al.*, 1994].

The biliary route of metabolism of 2-isopropyl-5-methylcyclohexanol and its corresponding ketone appear to be more important in rodents and dogs as compared to humans and rabbits. *l*-2-Isopropyl-5-methylcyclohexanone given to rabbits (1000 mg/kg bw) [Williams, 1940] is stereoselectively reduced to *d* stereoisomer of 2-isopropyl-5-methylcyclohexanol [Williams, 1940].

Urine samples collected over the course of four (4) days from rabbits given 1,000 mg/kg bw of isophorone (3,5,5-trimethyl-2-cyclohexen-1-one) *via* gavage showed several metabolites: the major conjugated metabolites includes 3,5,5-trimethyl-2-cyclohexen-1-ol (isophorol) formed by reduction of the ketone group and then conjugation with glucuronic acid and *cis*- and *trans*-3,5,5-trimethylcyclohexanol formed by hydrogenation of the endocyclic double bond, reduction of the ketone, and conjugation with glucuronic acid. In addition, 5,5-dimethyl-1-cyclohexene-3-one-1-carboxylic acid formed by methyl group oxidation at an exocyclic allylic position [Truhaut *et al*., 1970; Dutertre-Catella *et al.,* 1978].

The data clearly demonstrate that unsubstituted or alkyl-substituted cyclohexanones are readily absorbed and reduced to the corresponding cyclohexanol derivatives in a variety of animal species over a wide range of dose levels. The cyclohexanol derivatives are then conjugated with glucuronic acid and excretion mainly in the urine.

In summary, there is clear evidence that both the aliphatic linear- and branched-chain ketones and alkyl-substituted cyclohexanones in the KB4 and KB3 mixtures are readily absorbed, interconverted with their corresponding alcohols, and excreted primarily as the glucuronic acid conjugate of the alcohol. Given the consistent pattern of pharmacokinetics and metabolic fate, it is concluded that endpoint data for higher molecular weight linear aliphatic ketones and their corresponding alcohols and data on alkyl-substituted cyclohexanone and cyclohexanol derivatives are relevant to human hazard assessment of KB4 and KB3.

3 TEST PLAN

3.1 Chemical and Physical Properties

3.1.1 Melting Point

As expected, the increase in melting point for linear aliphatic ketones parallels and increase in molecular weight. The experimental melting points for 2-, 3-, and 5-nonanone, 2-, 3-, and 4-decanone, 2-, 4-, and 6-undecanone, 2-, 3-, and 4-dodecanone, and 2-pentandecanone increase from -4.85 ºC to 39.5 ºC [CRC Handbook of Chemistry and Physics, 2000; Clayton and Clayton, 1994; Alarie *et al*, 1995; Perry and Green, 1984; MPBPVP EPI Suite, 2000, Syracuse Research Corporation]. The model prediction melting points for the same group of linear aliphatic ketones are in the range from –5.85 ºC to 46.2 ºC [MPBPVP EPI Suite, 2000] indicating good agreement between model predictions and actual experimental data. The experimental melting points of the branched chain aliphatic ketones 5-methyl-3-heptanone and 5-ethyl-2-nonanone are reported to be –56.7 and -7.03 ºC, respectively [Clayton and Clayton, 1994; MPBPVP EPI Suite, 2000].The calculated melting points for the 3,3-, 2,3-, 2,6-, and 2,4-dimethylcyclohexanone are in the range from –1.07 ºC to –13.73 ºC while that for 3-methyl-5-propylcyclohexanone is 9.03 ºC [MPBPVP EPI Suite, 2000].

Based on the above data, the melting points of chemically-identified aliphatic ketones of the KB4/KB3 mixture are in the range –5 ºC to 40 ºC. Lower experimental and model calculated melting point values for C_8 branched-chain aliphatic ketones and alkyl-substituted cyclohexanones are expected.

3.1.2 Boiling Point

The experimental boiling points for linear aliphatic ketones reflect both the influence of carbon chain length and the position of the ketone functional group. For 2-alkanones the boiling points are in the range from 192 ºC - 195 ºC for 2-nonanone to 294 ºC for 2-pentadecanone [CRC Handbook of Chemistry and Physics, 2000; MPBPVP EPI Suite,

2000; Fragrance Materials Association; Perry and Green, 1984]. For nonanone isomers, the boiling point of 2-nonanone is 192 ºC - 195 ºC and that for 5-nonanone is 186 ºC - 188 ºC [CRC Handbook of Chemistry and Physics, 2000; Clayton and Clayton, 1994], with the decrease reflecting the decrease in polarity expected as the ketone function moves to the middle of the aliphatic chain. Similar trends are observed for other alkanones. Model predicted values for the boiling points of the homologous series from nonanone to pentadecanone are in good general agreement with experimental values (*i.e.*, 184.65 ºC for nonanone to 291.95 ºC for pentadecanone) [MPBPVP EPI Suite, 2000]. However, the current model cannot account for the effect of the position of the functional group on the carbon chain. Therefore, the predicted values for the boiling points of 2-, 3-, 4-, or 5-nonanone are the same.

The reported boiling point of 6-methyl-2-heptanone is 171 ºC. The calculated boiling point of 212.54 ºC for 5-ethyl-2-nonanone is consistent with those of other undecanone isomers [MPBPVP EPI Suite, 2000]. The reported experimental boiling points for the 3,3-, 2,3-, 2,4-, and 2,6-dimethylcyclohexanones are in the narrow range from 171 ºC to 179 ºC [CRC Handbook of Chemistry and Physics, 2000] and the calculated boiling point of 3-methyl-5-propylcyclohexanone is 224.46 ºC [MPBPVP EPI Suite, 2000].

Given that the measured and calculated boiling points values for linear aliphatic ketones are consistent and reflect the influence of molecular weight and polarity, the boiling points of the homologous linear aliphatic ketones are expected to be in the range from 186 ºC to 294 ºC. The measured and calculated boiling points of the branched-chain ketones (6-methyl-2-heptanone and 5-ethyl-2-nonanone) and alkyl-substituted cyclohexanone derivatives identified in the KB4/KB3 mixtures are in the range from 171 ºC to 225 ºC.

3.1.3 Vapor Pressure

The measured vapor pressure of 2-alkanones increases in the range from 0.642 mm Hg [Ohe, 1976] for 2-nonanone to 0.0216 mm Hg for 2-dodecanone [Perry and Green, 1984]. The vapor pressures of 2-, 3-, 4-, or 5-nonanone are similar. While 2-nonanone

exhibits a vapor pressure of 0.642 mm Hg [Ohe, 1976], 5-nonanone shows a vapor pressure of 0.552 mm Hg [Alarie *et al.*, 1995]. Similar vapor pressures have also been observed for 2-undecanone (0.0414 mm Hg) [Perry and Green, 1984] and 6-undecanone (0.50 mm Hg) [Engineering Science Unit, 1975]. The calculated vapor pressures, for the homologous series from nonanone to pentadecanone are 0.99 to 0.0036 mm Hg [MPBPVP EPI Suite, 2000] and in good agreement with measured values.

The vapor pressures of the four dimethylcyclohexanone isomers are calculated to be in the range from 1.04 to 1.66 mm Hg [MPBPVP EPI Suite, 2000]. The calculated vapor pressure for 3-methyl-5-propylcyclohexanone is 0.158 mm Hg [MPBPVP EPI Suite, 2000]. Given the good agreement between measured and calculated vapor pressures, it is concluded that the vapor pressures of ketones in the KB4/KB3 mixtures are in the range of 0.0036 to 1.6 mm Hg.

3.1.4 n-Octanol/Water Partition Coefficients

Experimental log K_{OW} values of 2-nonanone, 2-decanone, and 2-undecanone [Tanii *et al.*, 1986] are 3.14, 3.73, and 4.09 respectively. The calculated log K_{OW} values of 2.71, 3.21, and 3.69, respectively, for the same substances indicated that model values are similar to, but consistently less (approximately -0.4 units) than measured values [KOWWIN EPI Suite, 2000]. It should be emphasized that the calculated KOWWIN values are equivalent regardless of the position of the ketone. Values calculated based on a molecular fragment method [Hansch *et al.*, 1989] for 5-nonanone and 2-decanone (3.06 and 3.60, respectively) are in close agreement with experimental values.

The effect of the position of the ketone function on K_{OW} values may be evaluated from experimental and calculated data for 2-nonanone and 5-nonanone. The experimental and calculated K_{OW} values for 2-nonanone are 3.14 [Tanii *et al.*, 1986] and 3.21 [KOWWIN EPI Suite, 2000], respectively. The experimental log K_{OW} value for 5-nonanone is 2.88 [Abraham, 1994]. The K_{OW} values calculated by the molecular fragment method for 5-nonanone are 2.79 [Hansch *et al.*, 1967] and 3.06 [Hansch *et al.*, 1989]. The higher values for 2-nonanone compared to those of 5-nonanone may indicate increased octanol

solubility (higher log K_{OW}) for the longer alkyl chain in 2-nonanone. However, it is difficult to evaluate these data given the different experimental and calculated methods used. In any event, the small difference between the experimental or calculated K_{OW} values for 5-nonanone and 2-nonanone, indicate that the position of the ketone function has little impact on the log K_{OW}.

Based on the results of log K_{OW} determinations for a series of ketones, including 7-tridecanone (log K_{OW} = 5.17) using a molecular fragment method [Hansch and Leo, 1979], it is estimated that log K_{OW} of 2-dodecanone is 4.60. Similar to experimental and calculated values for other lower molecular weight ketones, the KOWWIN calculated log K_{OW} of 4.18 [KOWWIN EPI Suite, 2000] is slightly lower than values calculated by the molecular fragment method. Based on the above analysis, the log K_{OW} values for the isomers of nonanone, decanone, undecanone, and dodecanone are concluded to be 3.17, 3.73, 4.09, and 4.60, respectively. The calculated log K_{OW} of 5.66 [KOWWIN EPI Suite, 2000] for 2-pentadecanone is consistent with the trend of experimental and calculated values for lower homologues.

The calculated value of log K_{OW} for 6-methyl-2-heptanone is calculated to be 2.15 [KOWWIN EPI Suite, 2000]. The log K_{OW} values calculated by a molecular fragment method for the linear isomer, 2-octanone, are 2.52 [Hansch *et al.*, 1989] and 2.46 [Hansch and Leo, 1979]. Given that alkyl branching increases water solubility, the difference recorded for the straight and branched chain isomers is reasonable. Therefore, the log K_{OW} for 6-methyl-2-heptanone is concluded to be 2.15. Comparison of calculated log K_{OW} values for straight (2-undecanone, log K_{OW} 3.69) and branched-chain (5-ethyl-2-nonanone, log K_{OW} 2.94) ketones reveals a similar trend. The dimethylcyclohexanone derivatives are calculated [KOWWIN EPI Suite, 2000] to exhibit log K_{OW} value of 1.98 while 3-methyl-5-propylcyclohexanone exhibits a calculated log K_{OW} value of 2.94. Based on the above analysis, the ketones in KB4/KB3 exhibit log K_{OW} values in the range of 2-4. Only pentadecanone isomers in KB3, that account for only 5% of the mixture, exhibit a log K_{OW} value greater than 5.

3.1.5 Water Solubility

The experimental water solubility of 376 mg/L determined for 5-nonanone [Palit, 1947] is in good agreement with the calculated value of 284.4 mg/L [WSKOWWIN EPI Suite, 2000]. Other calculated values for 2-, 3-, 4-, and 5-nonanone are in the range from 170.6 to 396.1 mg/L [WSKOWWIN EPI Suite, 2000]. The water solubilities for the isomers of decanone is 46.4 to 131 mg/L, for undecanone is 19.7 to 43.0 mg/L, for dodecanone is 14.0 mg/L, and for pentadencanone is 0.468 mg/L. The calculated water solubilities of 6-methyl-2-heptanone and 5-ethyl-2-nonanone are determined to be 1,371 mg/L and 49.63, respectively, at 25 ^{o}C [WSKOWWIN EPI Suite, 2000]. The calculated water solubilities of the isomers of dimethylcyclohexanone and 3-methyl-5-propylcyclohexanone are determined to be 1,874 mg/L and 222.7, respectively, at 25 ^{o}C [WSKOWWIN EPI Suite, 2000]. With the exception of pentadecanone, the solubility range for aliphatic and alicyclic ketones in the KB4/KB3 mixtures is expected to be approximately 50-2000 mg/L.

3.1.6 New Testing Required

No further testing is required.

3.2 Environmental Fate and Pathways

3.2.1 Photodegradation

The measured half-life values for the reaction of 2-octanone, 2-nonanone, and 2-decanone with hydroxyl radicals based on an average atmospheric hydroxyl radical concentration of 5 $x10^5$ molecules/cm^3 have been reported to be 5.5, 6.3, and 6.8 hours, respectively [Wallington and Kurylo, 1987]. Calculated half-lives for the 2-nonanone and 2-decanone are 11.67 and 10.34 hours, respectively [AOPWIN EPI Suite, 2000]. The calculations are based on measured rate constants for radical reactions of OH with organic substrates [AOPWIN EPI Suite, 2000]. The short half-lives for the ketones are consistent with the presence of reactive *alpha*- and *beta*-hydrogens (hydroxyl radical-*beta* hydrogen 6-membered transition state) present in the aliphatic ketones. The calculated and measured values for rate constants for aliphatic ketones are consistently in the range of 10 X 10^{-12} to 10 X 10^{-13} cm^3/molecule-second while the half-lives are in the range from 5.5 to 12 hours. Also, calculated half-lives for the alkyl-substituted cyclohexanone derivatives and branched-chain ketones are in the range of 4.8 to 16 hours [AOPWIN EPI Suite, 2000]. Taken together these data support the conclusion that the ketones in KB4/KB3 mixtures will be rapidly degrade in the atmosphere.

3.2.2 Stability in Water

Hydrolysis is the reaction of organic molecules with water under acidic conditions to yield products in which new bonds to oxygen (OH) and hydrogen (H) are formed such as in the hydrolysis of esters to yield a carboxylic acid and an alcohol. Hydrolysis may also involve the addition of water to aldehydes or ketones to yield acetals or ketals under mild acid conditions. However, this addition of water is thermodynamically favorable only for low molecular weight aldehydes (*e.g.*, acetaldehyde) or ketones. The higher molecular weight ketones in KB4/KB3 do no form stable ketals. Therefore, the ketones are stable to water under ambient environmental conditions.

Another possible reaction of ketones in water involves the enolic hydrogen on the carbons bonded to the carbonyl function. Under conditions of high pH (pH greater than 10), the enolic proton is abstracted by base (OH^-) forming a carbanion intermediate that may react with other organic substrates (*e.g.*, ketones, esters, aldehydes) containing a center for nucleophic attack. The reactions, commonly recognized as condensation reactions, produce higher molecular weight products. Under ambient conditions of temperature, pH, and low concentration, these condensation reactions are unfavorable. Therefore, under environmental conditions, it is concluded that the ketones in the KB4/KB3 mixtures are stable.

3.2.3 Biodegradation

In a study adhering to OECD Guidelines, 5-methyl-2-hexanone was readily biodegradable (67% in 14 days) when tested using activated sewage sludge sewage [Springborn Laboratories, 2001].

2-Heptanone was reported to be biodegradable when tested with domestic activated sludge in the ISO BOD [Eastman Chemical Co., 1997b] or COD test [Eastman Chemical Co., 1997a]. Based on the BIOWIN Model, alkanones from C_9 to C_{15} are determined to be readily biodegradable by the Linear or Non-linear Biodegradation Probability Models [BIOWIN EPI Suite, 2000]. Given the consistency of the experimental data and that calculated for C_9 to C_{15} ketones, it can be concluded that these substances are readily biodegradable.

3.2.4 Fugacity

Transport and distribution in the environment were modeled using Level III Fugacity-based Environmental Equilibrium Partitioning Model [Mackay, 1991, 1996a, 1996b] through the EPA EPI Suite 2000 program. The input parameters used were molecular weight, melting point and boiling point.

The model predicts that linear aliphatic ketones are distributed mainly to the soil (48-67%), but are also distributed to water (16-36%) with the lower molecular weight ketones (nonanones) showing slightly greater distribution to the air (4-6%) than the higher molecular weight ketones (pentadecanones) (2%). Based on structural features of these substances, distribution to air and sediment (0.7-3.0%) are expected to be minimal for the major linear aliphatic ketones in the KB4/KB3 mixture. Half-lives in the environment are calculated to be less than a day in the air (13-30 hours), weeks (2-10) in water and soil, and months (1-3) in the sediment.

Model caluclations for the isomeric dimethylcyclohexanones, 3-methyl-5-propylcyclohexanone, 5-ethyl-2-nonanone, and 6-methyl-2-heptanone predict environmental fates similar to the linear aliphatic ketones discussed above. Based on the ready biodegradability data and the predicted half-lives in the various environmental compartments, it is concluded that the ketones in KB4/KB3 mixtures are not persistent in the environment.

3.2.5 New Testing Required

No further testing is required.

3.3 Ecotoxicity

3.3.1 Acute Toxicity to Fish

Experimental and calculated acute toxicity data for fish are available for 2-octanone [Veith *et al*., 1983; Broderius and Kahl, 1985], 2-nonanone [Geiger *et al.*, 1986], 5-nonanone [Veith *et al*., 1983; Geiger *et al.*, 1986], 2-decanone [Geiger *et al.*, 1986], 2-undecanone [Geiger *et al.*, 1986] and 2-dodecanone [Geiger *et al.*, 1986] (see Table 2). These values compared favorably with the LC50 values calculated for ketones as neutral organics in the ECOSAR model [ECOSAR EPI Suite, 2000].

TABLE 2 - ACUTE 96-HR LC50 VALUES IN FATHEAD MINNOW (FLOW-THROUGH METHOD)

Substance	Calculated 96-hour LC50, mg/L	Experimental 96-hour LC50, mg/L	Reference
2-Octanone	NA	63.0	Broderius and Kahl, 1985
2-Nonanone	22.68	15.2	Geiger *et al.*, 1986
5-Nonanone	22.68	31	Veith *et al*., 1983; Geiger *et al.*, 1986
2-Decanone	8.627	5.7	Veith *et al*., 1983; Geiger *et al.*, 1986
2-Undecanone	3.255	1.5	Geiger *et al.*, 1986
2-Dodecanone	1.20	1.18	Geiger *et al.*, 1986
2-Pentadecanone	0.061	NA	NA

Based on these values, it is concluded that the range of 96-hour LC50 values for the homologous series from 2-nonanone to 2-dodecanone is 31 to 1.18 mg/L. Based on the ECOSAR model it is anticipated that the minor amount (5%) of pentadecanone isomers in KB3 will exhibit the lowest LC50 (approximately 0.06 mg/L) [ECOSAR EPI Suite, 2000].

Acute 96-hour LC50 data on isomers and substances structurally related to 6-methyl-2-heptanone indicate an LC50 value between 50 and 100 mg/L for. In tests using a continuous flow-through method, 2-octanone and 6-methyl-5-hepten-2-one exhibit 96-hour LC50 values of 36mg/L and 85.7 mg/L, respectively [Veith *et al.*, 1983]. In a second flow through study, 2-octanone was reported to show a 96-hour LC50 value of 63 mg/L [Broderius and Kahl, 1985]. Also, the homologue, 5-methyl-2-hexanone exhibited a 96-hour LC50 value of 100 ul/L (80.2 mg/L) in a static test using fathead minnows [Eastman Kodak Co., 1978]. These values are in good agreement with the 96-hour LC50 value of 68.70 calculated for 6-methyl-2-heptanone by the ECOSAR model [ECOSAR EPI Suite, 2000]. For the other branched-chain isomer of undecanone, 5-ethyl-2-nonanone the calculated 96-hour LC50 is 3.788 mg/L [ECOSAR EPI Suite, 2000]. The experimental 96-hour LC50 of 3,5,5-trimethylcyclohexenone (220 mg/L) in bluegills determined under static conditions [Buccafusco *et al.*, 1981] compares favorably with the calculated values of 93.55 mg/L for 3,3-dimethylcyclhexanone and 102 mg/L for 2,3-, 2,4-, or 2,6-dimethylcyclohexanone determined by the ECOSAR model [ECOSAR EPI Suite, 2000]. The calculated 96-hour LC50 value of 14.95 mg/L for the more lipophilic cyclohexanone, 3-methyl-5-propylcyclohexanone, is consistent with other model predictions for more lipophilic alkyl-substituted cyclohexanones [ECOSAR EPI Suite, 2000].

Given the consistency of measured and calculated data for representative alkanones in the KB4/KB3 mixtures, it will not be necessary to perform additional acute fish toxicity tests.

3.3.2 Acute Toxicity to Invertebrates

Calculated aquatic invertebrate 48-hour LC50 values for nonanone, decanone, undecanone, dodecanone, and pentadecanone decrease in the order of 26.52, 10.04, 3.92, 1.52, to 0.084 mg/L [ECOSAR EPI Suite, 2000]. These values are consistent with, and similar to, the respective acute toxicity values calculated for fish [ECOSAR EPI Suite, 2000]. Also, the calculated 48-hour LC50 values for 6-methyl-2-heptanone (74.38 mg/L), 5-ethyl-2-nonanone (4.54 mg/L), 3,3-dimethylcyclohexanone (93.88 mg/L), and 2,3-, 2,4-, or 2,6-dimethylcyclohexanone (109.0 mg/L) are remarkably similar to the calculated 96-hour LC50 values for fish.

The experimental 96-hour LC50 value and 96-hour EC50 value of the homologue 5-methyl-2-hexanone in *Daphnia magna* are reported to be greater than 100 ul/L (greater than 80 mg/L) [Eastman Kodak Co., 2000]. This value is consistent with the ECOSAR calculated value of 68.70 mg/L for 6-methyl-2-heptanone and with the experimental 24-hour LC50 value (170mg/L) for 5-methyl-2-hexanone in *Daphnia magna* [Bringmann and Kuehn, 1977]. Other linear (3-octanone) and cyclic (2-methylcyclohexanone) ketones exhibit 24-hour LC50 values (517 and 435 mg/L, respectively) that indicate a low order of acute toxicity for the component ketones in the KB4/KB3 mixtures [Bringmann and Kuehn, 1977].

In 48-hour test using *Tetrahymena pyriformis*, the EC50 values for 4-heptanone, 2-octanone, 5-nonanone, and 2-decanone were reported to be 679, 224, 145, and 49.3 mg/L, respectively [Schultz *et al.*, 1990]. In a 40-hour static test, again using *Tetrahymena pyriformis*, the 50% growth inhibitory concentrations of 2-nonanone, 2-decanone, 2-undecanone, and 2-dodecanone are reported to be 33.26, 44.21, 5.76, and 4.19 mg/L, respectively [Schultz, 1997]. Given that these EC50 values were measured over a shorted time period, higher EC50 values are anticipated.

Based on the experimental and calculated values for ketones in the KB4/KB3 mixture, with the exception of pentadecanone isomers, no ketone is predicted to exhibit a 96-hour LC50 value less than 1.0 mg/L.

3.3.3 Acute Toxicity to Aquatic Plants

Experimental acute toxicity data for aquatic plants were available for 2-heptanone and 5-methyl-2-hexanone. 2-Heptanone [Eastman Kodak Co., 1998] and 5-methyl-2-hexanone [Eastman Kodak Co., 2001a] were tested in *Scenedesmus subspicatus* (algae) and a 72-hour EC50 value of 42.7 mg/L was determined in both tests. The experimental values are on the same order of magnitude as the ECOSAR calculated value of 98.3 mg/L for 2-heptanone [ECOSAR EPI Suite 2000].

Model calculated 96-hour EC50 values for all isomers of nonanone, decanone, undecanone, dodecanone, and pentadecanone decrease in the order 16.62, 6.728, 2.701, 1.077, and 0.065 mg/L, respectively. Also, calculated 96-hour EC50 values for isomers of dimethylcyclohexanone and 6-methyl-2-heptanone are 62.67 and 46.90 mg/L, respectively [ECOSAR EPI Suite, 2000]. Based on the consistency of the measured and calculated values for 2-heptanone and 5-methyl-2-hexanone, the ECOSAR calculated values for higher homologues are reliable. They indicate that in the homologous series from C_7-C_{12} the 96-hour EC50 values are in the range from 100 to greater than 1 mg/L.

3.3.4 New Testing Required

No further testing is required.

3.4 Human Health

Based on the consistent pattern of pharmacokinetics and metabolic fate that indicates ketones and alcohols are interconvertible *in vivo*, it is concluded that endpoint data for higher molecular weight linear aliphatic ketones and their corresponding alcohols and data on alkyl-substituted cyclohexanone and cyclohexanol derivatives are relevant to human hazard assessment of KB4/KB3 mixtures.

3.4.1 Acute Toxicity

Given the relatively low volatility of higher molecular weight ketones, acute toxicity *via* the oral and dermal routes would be more significant than *via* the inhalation route of exposure. Numerous oral, dermal, and inhalation LC50 values for linear aliphatic and alicyclic ketones have been reported in rats, mice, and rabbits. Overall, they exhibit a low acute toxic potential. Oral and dermal LC50s tended to exceed 5,000 mg/kg, with some oral LD50 values approaching 20,000 mg/kg.

For 2-nonanone, the rat oral LC50 was reported to be greater than 5,000 mg/kg bw [Moreno, 1980] in rats and 7,879 mg/kg [Tanii *et al*, 1986] in ddY mice. The oral LD50 value of 3-nonanone (LD50 = 5270 mg/kg) [Hoffman-Laroche, 1967] is similar to that of 2-nonanone. For 2-decanone, the rat oral LC50 value was reported to be 7,940 mg/kg [Tanii *et al.*, 1986]. The oral and dermal acute LD50 values of 2-undecanone are reported to exceed 5,000 mg/kg [Levenstein, 1974]. This oral LD50 value is consistent with another oral LD50 value of 19,448 mg/kg [Tanii *et al*., 1986] reported for 2-undecanone. The oral LD50 value for 2-tridecanone is also reported to be greater than 2,000 mg/kg [Dragoco, 2000].

Oral and dermal LC50 values for branched chain ketones are in the same range as for linear aliphatic ketones. The oral and dermal LD50 of 6-methyl-5-hepten-2-one is reported to be 4,100 mg/kg and greater than 5,000 mg/kg, respectively [Keating, 1972]. In another study on the same substance the oral LD50 was reported to be 4,200 ul/kg while, in an inhalation study, no deaths were recorded in rats exposed for 8 hours to an

atmosphere saturated with 6-methylheptenone at 20 ^{o}C [BASF, 1974]. The oral and inhalation LD50 of 3,5,5-trimethylcyclohexenone in Wistar rats is reported to be 3,450 mg/kg and 7 mg/L (1291 ppm), respectively [Exxon Chemical Americas, 1982].

Given the current database of information, it is concluded that the aliphatic and alicyclic ketones in the KB4 mixture are of low acute oral or dermal toxicity. It will not be necessary to perform additional acute toxicity tests.

3.4.2 *In vitro* and *In vivo* Genotoxicity

Representative aliphatic and alicyclic ketones have been tested in *in vitro* bacterial and mammalian cell lines and have shown no mutagenic or genotoxic potential. Similar results have been reported for the ketones and corresponding alcohols in *in vivo* assays. These findings confirm that the aliphatic ketones and alkyl-substituted cyclohexanones in the KB4/KB3 mixtures exhibit a low genotoxic potential.

3.4.2.1 In vitro Genotoxicity

Ames assays were performed on four aliphatic ketones of chain length greater than C_8. 2,6-Dimethyl-4-heptanone [Mortelmans *et al*., 1986], 6-methyl-5-hepten-2-one [Florin *et al*., 1980], and 6,10-dimethyl-2-undecatrienone [Florin *et al*., 1980] show no evidence of mutagenicity in TA98, TA100, TA1535, TA1537 and TA1538 strains of *Salmonella typhimurium*.

In vitro mutagenicity Ames testing has been performed with three alkyl-substituted alicyclic ketones. Negative results were reported in the standard Ames assay when various strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) were incubated with 3,5,5-trimethylcyclohexenone [Mortelmans *et al.*, 1986], 2,2,6-trimethylcyclohexanone [Florin *et al.*, 1980] (in TA 98 and TA100 only), or tetramethylethylcyclohexanone [Wild *et al.*, 1983] with or without S-9 metabolic activation.

3.4.2.2 *In Vivo Genotoxicity*

When 2-hexylidene cyclopentanone, tetramethylethylcyclohexanone, or 3,5,5-trimethylcyclohexenone were fed to adult *Drosophila melanogaster* for 3 days no mutations were observed [Foureman *et al.*, 1994; Wild *et al.*, 1983]. In addition, negative results were obtained when *Drosophila melanogaster* were injected with a single dose of 12,500 micrograms 3,5,5-cyclohexenone [Foureman *et al.*, 1994].

There was no increase in the frequency of micronucleated polychromatic erythrocytes in the bone marrow of male or female CD-1 mice administered 498 mg/kg bw of 3,5,5-cyclohexenone by intraperitoneal injection [O'Donoghue *et al.*, 1988] or in NMRI mice intraperitoneally injected with 166, 333 or 500 mg/kg bw of 2-hexylidenecyclopentanone or 180, 307 or 450 mg/kg bw of tetramethylethylcyclopentenone [Wild *et al.*, 1983].

Intraperitoneal injection on 3 consecutive days with up to 1,000 mg/kg bw of 2-isopropyl-5-methylcyclohexanol did not induce micronuclei in mouse bone marrow [Shelby *et al.*, 1993]. In a host-mediated assay, mice were gavaged with up to 3,000 mg/kg bw of 2-isopropyl-5-methylcyclohexanol in a single-dose study or up to 1,150 mg/kg bw/day of 2-isopropyl-5-methylcyclohexanol in a 5-day study [Food and Drug Administration, 1975]. After the last dose, mice were intraperitoneally injected with an indicator organism (*Salmonella typhimurium* strains G46 and TA1530, or *Saccharomyces cervisiae* D3). The peritoneal exudate was plated and incubated for assessment of mutation and recombinant frequencies. No significant increase in mutant and recombinant frequency at any dose or exposure period in *Salmonella typhimurium* G46. In *Saccharomyces cervisiae* D3, an elevation of recombinant frequency was reported in the 5-day exposure study, but not in the single-exposure study. At the highest dose tested in *Salmonella typhimurium* TA1530, in the single-dose study, a significant increase in mutant frequency was reported. This was not reported in the 5-day study. *In vitro* tests using the same organisms were all negative.

In a chromosomal aberration study, rats were gavaged with up to 3,000 mg/kg bw of 2-isopropyl-5-methylcyclohexanol as a single exposure or up to 1,150 mg/kg bw/day of 2-isopropyl-5-methylcyclohexanol for 5 days [Food and Drug Administration, 1975].

Analysis of bone marrow demonstrated that exposure to 2-isopropyl-5-methylcyclohexanol as a single dose or for a 5-day period did not induce chromosomal aberrations.

3.4.2.3 Conclusions

The *in vitro* studies, on linear and branched-chain aliphatic ketones and alicyclic ketones, show no evidence of genotoxicity. The *in vivo* studies, performed on alkyl-substituted alicyclic ketones and structurally related alcohols, also show no evidence of genotoxicity. Therefore, it is concluded that, the mixture of ketones in KB4/KB3 is of low genotoxic potential.

3.4.3 Repeat Dose Toxicity

Repeat-dose toxicity studies are available for 2-nonanone, 2,6-dimethyl-4-heptanone, 5-nonanone, an undecanone isomer, 2,8-dimethyl-5-nonanone, 3,5,5-trimethyl cyclohexenone, 2-pentadecanone, a mixture of alkyl-substitued cyclohexanones and cyclohexanols, and the alkyl-substituted cyclohexanol derivative, 2-isopropyl-5-methylcyclohexanol. The most consistent pathologic effect in both subchronic and chronic studies was the appearance of hyaline droplet nephropathy in male rats.

Groups of 3 Charles River CD, COBS male rats were administered 2-nonanone (*i.e.*, methyl heptyl ketone) *via* gavage, 5 days per week for 3 weeks at doses of 1,000, 2,000, or 4,000 mg/kg bw. Individual body weights and feed consumption were recorded on days 0, 3, 7, 14 and 20 of treatment. All animals were observed daily for clinical signs of toxicity. Necropsy was performed on all test animals, and tissues were collected for histological examination.

Upon necropsy, no gross compound-related changes were detected at any dose level. Histological examination revealed compound related changes in the stomach and liver at the 2,000 and 4,000 mg/kg bw/day levels, and in the lungs, kidneys, bladder, adrenal glands, bone marrow, brain, and mesenteric fat at the 4,000 mg/kg bw/day level. However, it was not reported whether or not these effects were statistically significant.

In the stomach, hyperplasia of the epithelium of the non-glandular mucosa was observed with at varying degrees, which were thought to reflect the amount of contact the test material had with the epithelium and the selection of the tissue specimens for examination. Liver changes were characterized by hepatocyte hypertrophy. In the 4,000 mg/kg bw/day group, lungs showed minor acute bronchitis and congestion, edema, and atelectasis; the urinary system had dilatation of the lumena of the renal tubules and multiple hemorrrhages in the bladder (1 rat); the adrenal gland was congested; bone marrow and brains were congested in 2 or 3 rats, respectively; and atrophy of the mesenteric adipose tissue occurred in 1 rat. In the 1,000 mg/kg test group, no gross or histopathologic compound-related changes were identified [Krasavage and O'Donoghue, 1979].

2,6-Dimethyl-4-heptanone (67.0% purity; *i.e.*, diisobutyl ketone) was administered to 8 male Charles River rats by gavage for 90 days at a dose of 0 or 2,000 mg/kg bw/day. Following the dosing period, liver, kidney, brain, adrenal glands, testes, heart and spleen weights were recorded and relative organ weights calculated. Hematology and clinical chemistry was performed and results were comparable to controls. Absolute and relative liver weights, relative kidney weights, and absolute and relative adrenal gland weights were statistically greater than controls. Absolute, but not relative brain and heart weights were significantly depressed. All other organ weights were comparable to controls.

No compound related gross pathologic changes were identified. Histopathology examinations were also conducted on the test animals and revealed compound related changes in the stomach, liver, and kidneys. In the stomach, all animals showed hyperkeratosis or hyperkeratosis with pseudoepitheliomatous hyperplasia associated with irritation from direct contact by the solvent. In the liver, minor or moderate hepatocyte hypertrophy was observed. In the kidney, hyaline droplet formation was present in the proximal tubular epithelium suggesting *alpha*-microglobulin-type nephropathy. There was also a minor occurrence of regenerating tubular epithelium and tubular dilation with casts [O'Donoghue and Krasavage, 1980]. A similar toxicologic profile including the presence of hyaline droplet formation was reported after 2,000 mg/kg of 5-methyl-2-hexanone [Eastman Kodak Co., 1979] or 4000 mg/kg of 2,8-dimethyl-5-nonanone

(99.5%) [O'Donoghue and Krasavage, 1980] was given to rats 5 days per week for 90 days.

In a study limited to the neurotoxic evaluation, groups of Charles River male rats were given 233 mg/kg of 5-nonanone (98.25%) 5 days weekly for 90 days. There was no evidence of neurotoxic activity [O'Donohogue J. L. *et al.*, 1982]. In an oral gavage study, 2,000 mg/kg of impure 2-nonanone (impurity, 5-nonanone) when administered to rats for 90-days showed evidence of "giant axonal swelling" neuropathy. This neurotoxic phenomenom is typical of ketones that can be readily metabolized to *gamma* diketones (*i.e.*, 5-nonanone) [O'Donoghue and Krasavage, 1980]. However, when fed to rats at lower dietary levels, 5-nonanone showed no evidence of neurotoxicity.

In a 14 day dietary study, 2-pentadecanone was added to the diet of groups of male and female Fischer 344 rats at levels calculated to provide an average daily intake of 10 mg/kg bw. Based on measurement of body weight, food consumption, gross examination, liver and kidney weights, and microscopic examination of the liver and kidneys, no effects were observed [VanMiller and Gill, 1987].

A sample of an essential oil, predominantly containing a mixture of 2-isopropyl-5-methylcyclohexanone and 2-isopropyl-5-methylcyclohexanol isomers that accounts for greater than 85% of the mass of the oil, was used in the 28 day study [Serota, 1990] and reproductive/developmental screening [Hoberman, 1989, robust summary in reproductive toxicity section] study cited below. Based on a gas chromatogram (FIS detector), the oil was determined to contain:

- 46.8% (1 *alpha*, 2 *beta*, 5 *alpha*)-2-isopropyl-5-methylcyclohexanol
- 3.97% (1 *alpha*, 2 *alpha*, 5 *alpha*)-2-isopropyl-5-methylcyclohexanol
- 0.86% (1 *beta*, 2 *beta*, 5 *alpha*)-2-isopropyl-5-methylcyclohexanol
- 21.81% (2 *beta*, 5 *alpha*)-2-isopropyl-5-methylcyclohexanone
- 3.07% (2 *beta*, 5 *beta*)-2-isopropyl-5-methylcyclohexanone
- 5.11% (1 *alpha*, 2 *beta*, 5 *alpha*)-2-isopropyl-5-methylcyclohexyl acetate
- 1.55% (1 *beta*, 2 *beta*, 5 *beta*)-2-isopropyl-5-methylcyclohexyl acetate

The other constituents accounting for approximately 10% of the oil included aliphatic terpene hydrocarbons (*e.g.*, *alpha*-pinene) and ethers (eucalyptol) [Vollmuth, 1989, no robust summary provided].

The sample was administered by gavage in corn oil to groups of Sprague-Dawley rats at dose levels of 0, 100, 200, or 400 mg/kg bw/day for 29 or 30 days [Serota, 1990]. Clinical signs, body weights and food consumption were monitored. At necropsy, organ weights (brain, spleen, liver, heart, kidneys, testes with epididymides, adrenals, ovaries, and pituitary) were measured, and tissues (26) were preserved in 10% formalin. All tissues from the control and high-dose groups and tissues from the heart, liver, kidneys, and gross lesions from the low- and mid-dose group were embedded in paraffin, stained with hematoxylin and eosin, and examined microscopically. All animals survived to study termination with high-dose males showing increased incidence of urine staining during clinical observations. Except for a non-statistically significant decrease in mean body weight in high-dose males, there were no statistically significant differences in body weight or food consumption between treated and control groups. A significant decrease in serum glucose levels was reported in the mid- and high-dose males that the authors, in part, attribute to change in nutritional status as revealed by a decreased body weights in the high-dose group. A treatment-related increase in alkaline phosphatase also was reported in high-dose males. Measurement of body weight, food consumption, hematology and clinical chemistry parameters revealed no significant changes between test and control female rats. There were statistically significant increases in relative kidney weights in high-dose males. Histopathological findings revealed renal tubule protein droplets in all groups of treated male rats. The authors considered these findings related to the lysosomal handling of *alpha*-2-microglobulin, a protein specific to the male Sprague-Dawley rat. Absolute and relative liver weights in high-dose females also were significantly increased but these changes were not confirmed by histopathological examination. There was no histopathology of tissues from reproductive organs of males (testes with epididymis) or female (ovaries). Based exclusively on the renal pathology reported in all dosed groups of male rats, the authors concluded that the no observable

adverse effect level (NOAEL) for the sample is less than 100 mg/kg bw/day in male rats and 400 mg/kg bw/day in female rats.

The National Toxicology Program (NTP) conducted a chronic two-year bioassay on 3,5,5-trimethylcycloheneone (isophorone) using the standardized NTP protocol in F344/N rats. Doses were determined from the results of a prior 13-week subchronic toxicity study.

In a two-year study dose levels of 0, 250 or 500 mg/kg bw/day of 3,5,5-trimethylcycloheneone were given to groups of F344/N rats (50/sex/group) by gavage in corn oil 5 days a week daily for 103 weeks [NTP, 1986; Bucher *et al.*, 1986]. Food and water were provided *ad libitum*. Moribund animals were euthanized. Weights were recorded weekly and at the termination of the experiment survivors were sacrificed and necropsies performed. No clinical signs of toxicity were reported. Gavage errors accounted for a significant number of deaths (36/300) in both male and female rats.

Nephropathy was noted in both test and control rats of both sexes after natural death or at termination. In test animals, increased incidence of mineral deposits in renal collecting ducts (31/50, 62% and 20/50, 40%), and tubular cell hyperplasia (1/50, 2% and 4/50, 8%), adenomas (0/50 and 2/50, 8%), and adenocarcinomas (3/50, 6% and 1/50, 2%) were observed in male rats at 250 mg/kg bw/day and 500 mg/kg bw/day, respectively but not in female rats (see Table 3). Tubule mineralization was characterized by basophilic aggregates found in the medullary collecting ducts, often occurring coincidentally with lesions of chronic nephropathy. Authors of the NTP report concluded the following: "Under conditions of these 2-year gavage studies, there is some evidence of carcinogenicity of 3,5,5-trimethylcycloheneone in the male F344/N rat as shown by the occurrence of renal tubular cell adenomas and adenocarcinomas in animals given 250 or 500 mg/kg/d..." [NTP, 1986; Bucher *et al*., 1986].

TABLE 3 - INCIDENCES OF RENAL NEOPLASMS ASSOCIATED WITH ADMINISTRATION OF 3,5,5-TRIMETHYLCYCLOHEXENONE TO RATS BY GAVAGE FOR 103 WEEKS

		Control	250 mg/kg	500 mg/kg
1.	Male Rats			
	Nephropathy	49/50	47/50	46/50
	Tubule mineralization	1/50	31/50	20/50
	Renal Tubule Hyperplasia	0/50	1/50	4/50
	Renal Tubule Adenoma*	0/50	0/50	2/50
	Renal Tubule Adenocarcinoma*	0/50	3/50	1/50
2.	Female Rats			
	Nephropathy	21/50	39/50	32/50
	Tubule mineralization	10/50	4/50	2/50
	Renal Tubule Hyperplasia	0/50	0/50	1/50
	Renal Tubule Adenoma*	0/50	0/50	0/50
	Renal Tubule Adenocarcinoma*	0/50	0/50	0/50

* Historical incidence of tubular cell adenoma or adenocarcinoma: 4/1091 (0.4%) $p < 0.05$.

B6C3F1 mice were fed diets containing 0, 930, 1870, 3750, 7500, or 15,000 ppm *dl*-2-isopropyl-5-methylcyclohexanol (approximately 0, 140, 281, 563, 1125 or 2,250 mg/kg bw/day of *dl*-2-isopropyl-5-methylcyclohexanol, respectively) for 13 weeks [National Cancer Institute, 1979]. Necropsies were performed on all animals at the end of the study. Histopathological examination was performed on tissues from selected animals. Six mice (sex not specified) died during the study but the deaths could not be attributed to compound administration. Final mean body weights of the male mice and female mice were not statistically different from those of the controls except for the high-dose female group which showed statistically significant decreased body weights. A slight increase in the incidence of perivascular lymphoid hyperplasia and interstitial nephritis was reported in female mice given the two highest dose levels. No adverse effects were reported for male or female mice administered 140, 281, or 563 mg/kg bw/day of *dl*-2-isopropyl-5-methylcyclohexanol.

A carcinogenicity study was conducted in which groups of B6C3F1 mice of each sex were fed diets containing 0, 2,000 or 4,000 ppm *dl*-2-isopropyl-5-methylcyclohexanol

(approximately 0, 300, or 600 mg/kg bw/day, respectively) 103 weeks [National Cancer Institute, 1979]. Necropsies and histological examinations were performed on all animals at the termination of the study and on those found dead during the study. The mean body weights of the treated mice were slightly lower than those of controls. Survival of the treated male mice and low-dose female mice was similar to the vehicle control animals; however, survival of the high-dose group of female mice was significantly less than that of the control animals but was not accompanied by any evidence of toxicity. There was no evidence of neoplastic or nonneoplastic lesions of the male (penis, prepuce, preputial gland, prostate, or epididymis) or female (uterus, endometrium, or ovaries) reproductive system. An increase in the incidence of hepatocellular carcinomas was observed in high-dose male mice, but was not statistically different from that observed historically in mice of that age and strain (Haseman *et al*., 1986; no robust summary provided). A low incidence of alveolar/bronchiolar adenomas of the lung was observed in treated females but was not statistically different from the incidence of this neoplasm in historical control groups. Under the conditions of this study, the authors concluded that *dl*-2-isopropyl-5-methylcyclohexanol was not carcinogenic and did not produce any organ-specific toxicity for either sex of B6C3F1 mice at dose levels up to 600 mg/kg bw/day.

Fischer 344 rats were fed diets containing 0, 930, 1870, 3750, 7500, or 15,000 ppm *dl*-2-isopropyl-5-methylcyclohexanol (approximately 0, 93, 187, 375, 750 or 1500 mg *dl*-2-isopropyl-5-methylcyclohexanol/kg bw/day, respectively) for 13 weeks National Cancer Institute, 1979]. Necropsies were performed on all animals at the end of the study. Histopathological examination was performed on tissues from selected animals. Final mean body weights of the male and female rats at all dose levels were similar to those of the controls. A slight increase in the incidence of interstitial nephritis was observed in high-dose male rats. No adverse effects were reported for male or female rats administered up to 750 mg/kg bw/day of *dl*-2-isopropyl-5-methylcyclohexanol.

Fischer 344 rats of each sex were fed diets containing 0, 3,750, or 7,500 ppm *dl*-2-isopropyl-5-methylcyclohexanol (approximately 0, 187, or 375 mg *dl*-2-isopropyl-5-methylcyclohexanol/kg bw/day, respectively) for 103 weeks [National Cancer Institute, 1979]. Necropsies and histological examinations were performed on all animals at the

termination of the study and on those found dead during the study. The mean body weights of treated rats were slightly lower when compared to the controls. Microscopic examination of tissues of test animals failed to reveal any evidence of neoplastic or nonneoplastic lesions, including those of the male (*e.g.*, penis, scrotum, prostate, mammary gland, or epididymis) or female (uterus, vagina, mammary gland, endometrium, or ovaries) reproductive system. Survival of the treated rats was similar to the control animals. Chronic inflammation of the kidney observed in the dosed older males was not considered by the authors to be related to the administration of *dl*-2-isopropyl-5-methylcyclohexanol since the effect is commonly observed in aged male Fischer 344 rats. There was no increase in the incidence of neoplasms of dosed females compared to that of control animals. In treated females, fibroadenomas of the mammary glands occurred at a lower incidence than in the control group. Alveolar/bronchiolar adenomas or carcinomas were reported only for the female control rats. Under the conditions of this study, the authors concluded that *dl*-2-isopropyl-5-methylcyclohexanol was neither carcinogenic nor toxic for either sex of Fischer 344 rats at dose levels of up to 375 mg/kg bw of *dl*-2-isopropyl-5-methylcyclohexanol.

Since publication of the variety of subchronic and chronic studies on aliphatic and alicyclic ketones, the mechanism of action associated with the formation of *alpha*-2-microglobulin in male rats has been extensively studied. These research studies are applicable to any substance exhibiting *alpha*-2-microglobulin-type nephropathy. Therefore, no robust summaries have been prepared for the studies cited below.

It has been clearly demonstrated that renal lesions, which were also observed in numerous NTP studies, resulted from the accumulation of aggregates of *alpha*-2-microglobulin (a low molecular-weight protein synthesized in the liver) and test agents or its metabolites in the P2 segment of the renal proximal tubule. This phenomenon was initially observed in the male F344/N rat [Strasser *et al.*, 1988; Borghoff *et al.*, 1990] but has now been identified in other well-recognized strains of laboratory rats [Hildebrand *et al.*, 1997; Saito *et al.*, 1996].

The gene that encodes *alpha*-2-microglobulin has been isolated and the sequence deduced [Untermann *et al*., 1981]. These proteins are expressed in the liver under hormonal control [Roy and Neuhaus, 1967; Wang and Hodgetts, 1998]. *alpha*-2-Microglobulin belongs to the *alpha*-2-microglobulin super family of proteins that are characterized by a unique hydrophobic binding pocket. The lesions do not develop in the female rat or in humans [Bucher *et al*., 1986]. Subsequent investigations have shown that the *alpha*-2-microglobulin nephropathy found in the male rat does not develop in mammals that do not express the hepatic form of *alpha*-2-microglobulin [Swenberg *et al.*, 1989; Dietrich and Swenberg, 1991], mice [Bucher *et al*., 1986; Lehman-McKeeman and Caudill, 1994] and dogs [Webb *et al*., 1990].

Transgenic mice that express rat *alpha*-2-microglobulin were tested for their ability to form hyaline droplets and develop nephropathies similar to their adult male rat counterparts [Lehman-McKeeman and Caudill, 1994]. This study involved male rats as positive control, transgenic C57BL/6J mice as experimental group and native C57BL/6 mice as negative controls. The animals at age 70-75 days were placed in metabolic cages and received 150 mg/kg bw/day of *d*-limonene in corn oil by gavage for three days. Limonene is a potent inducer of renal nephropathy in adult male rats [Environmental Protectioin Agency, 1991; NTP, 1990]. Twenty-four (24) hours after the last dose the animals were sacrificed and the kidneys analyzed for evidence of nephropathy. Hyaline droplet formation was evaluated on a subjective scale, size and intensity (0-4) multiplied by tubular loading (0-3) for an overall scale of 0-12 with 12 being the most severe. In the absence of *d*-limonene the control groups transgenic mice and rats showed a hyaline droplet score of 1+/-0 and 6+/-0.5, respectively. The test transgenic mice and rats showed a hyaline droplet score of 2.5+/-0.3 and 11+/-1.3, respectively upon dosing with *d*-limonene. The native mice developed no signs of hyaline droplet formation and tested negative for presence of *alpha*-2-microglobulin in their urine. The authors assert that based on the data presented "*alpha*-2-microglobulin is the only protein that is involved in the etiology of hyaline droplet nephropathy".

An increase in the kidney-type-*alpha*-2 microglobulin was seen in male Sprague-Dawley rats when these animals were administered 200 mg/kg bw/day of isophorone by gavage

for 7 days. The increases in the urinary kidney-type- *alpha*-2-microglobulin are dose-dependent and parallel-elevated accumulation in the kidney cells [Saito *et al.*, 1996].

In another study, adult male Wistar rats were administered two groups of chemical compounds, including 138 mg/kg bw of isophorone, potassium bromate, 2-propanol and a series of benzene and anthracene derivatives, to study induction of accumulation of *alpha*-2-microglobulin and structure-activity relationships. A monoclonal antibody against *alpha*-2-microglobulin was employed in a competitive ELISA procedure to determine its concentration in urine or tissue samples without purification. Plasma concentrations of *alpha*-2-microglobulin were not significantly increased by any of the test compounds at 1 mmol/kg bw. Kidney tissue concentrations were found to be 297-300% higher than that of controls. The hyaline droplet accumulating (HDA) potential was dependent on the test compound but there was no relationship between HDA activity and the structure or the pathway used to metabolize the test substance [Hildebrand *et al.*, 1997].

The above studies depend exclusively on histopathologic evidence to detect *alpha*-2-microglobulin nephropathy. An *in vitro* assay based on the prerequisite of a chemical or metabolite to *alpha*-2-microglobulin has been developed that predicts, in greater than 90% (22/24) of the substances tested, the ability to induce *alpha*-2-microglobulin nephropathy [Lehman-McKeeman and Caudill, 1999]. *d*-Limonene-1,2-epoxide is well characterized as an *alpha*-2-microglobulin nephropathy inducer and has a steady state binding constant (K_d) of 5×10^{-7} M [Lehman-McKeeman *et al.*, 1989]. Based on this, a competitive binding assay was developed with [^{14}C]-d-limonene-1,2-epoxide and male rat urinary protein concentrate. Homogenous *alpha*-2-microglobulin was obtained from adult male rats [Lehmann-McKeeman and Caudill, 1992]. The assay was run with three series of competitive inhibitors terpenes (5), decalin/decanes/decanones (10), and halobenzenes (8). Total male urinary protein was incubated for 1 hour with the test materials, ranging from 0.001 to 3000 microM, and 0.5 microM [^{14}C]-d-limonene-1,2-epoxide. The ability of the test materials to displace 50% of the radiolabelled limonene epoxide from the protein was evaluated and IC50 values were calculated. An IC50 value of less than or equal to 100 microM for the terpene and decalin/decanone series is

considered predictive of *alpha*-2-microglobulin droplet formation. 2-Decanone was predicted to exhibit *alpha*-2-microglobulin droplet activity in male rats. Substances with an IC50 calculated at higher than 100 microM in the competitive binding assay were subjected to microsomal oxidation to generate metabolites that would bind to *alpha*-2-microglobulin. Three of the halobenzenes 1,2-, 1,4-, and 1,3-dichlorobenzene tested positive for *alpha*-2-microglobulin binding when incubated in the presence of rat liver microsomes. Parallel *in vivo* tests were performed in rats and hyaline droplet formation in the kidney was assessed to confirm the *in vitro* results. The authors concluded that the *in vitro* assay is greater than 90% predictive of *alpha*-2-microglobulin nephropathy induction in male rats without being invasive or requiring additional animal testing [Lehman-McKeeman and Caudill, 1999].

To further investigate kidney tissue concentration of *alpha*-2-microglobulin in the lysosomal portion, intact kidney lysosomes were isolated from untreated or 2,2,4-trimethylpentane (TMP)-treated rats and their ability to take up *alpha*-2-microglobulin was compared. It was found that *alpha*-2-microglobulin could be directly taken up in the presence of the heat shock cognate protein (*hsc*73). Hsc73 contributes to the normal degradation, lysis, of *alpha*-2-microglobulin in rat kidney and liver. However, in the presence of a chemical (TMP) known to induce aggregation of *alpha*-2-microglobulin, the activity of this pathway is increased. This may be due to an increase in the concentration of a receptor protein in the lysosomal membrane, which accelerates the uptake of cytosolic protein, *alpha*-2-microglobulin [Cuervo *et al.*, 1999].

While humans produce low molecular weight serum proteins, which are reabsorbed by the kidney, there is no evidence that *alpha*-2-microglobulin is produced [Olson *et al.*, 1990]. Urine collected from adult male rats and humans revealed no evidence that *alpha*-2-microglobulin production occurs in humans [Olson *et al.*, 1990].

It is unknown whether any human serum proteins possess a binding site similar to that of *alpha*-2-microglobulin. Although this is a possibility, it appears remote, since female rats, mice, and dogs do not show the renal changes noted in male rats exposed to isophorone. It should be noted that there is a class of human proteins referred to as the *alpha*-2-

microglobulin related proteins. They appear to have no functional relationship to the adult male rat urine proteins. The human protein has a higher molecular weight, 25 kDa and is a component of a neutrophil gelatinase complex [Kjeldsen *et al.*, 2000; Triebel *et al.*, 1992]. An extensive review of the current scientific literature and genome databases reveals no native protein or biological entity that acts as a nephropathy agent like mature male rat *alpha*-2-microglobulin. The accumulated evidence indicates that it is the unique anatomical, physiological, and biochemical properties of the male rat kidney, especially the proximal convoluted tubule, that allows isophorone to interfere with renal processing of the strain-specific *alpha*-2-microglobulin. Therefore, this process is not predictive of human carcinogenicity. In a comprehensive review of *alpha*-2-microglobulin nephropathy and associated renal tubule tumors produced in the male rat exposed to isophorone and other simple ketones and hydrocarbons (*e.g.*, limonene, decalin and methyl isobutyl ketone), it was concluded that the F344/N male rat is not an appropriate model for assessing human renal carcinogenic risk [Environmental Protection Agency, 1991]. After careful review, it has been concluded that the mechanisms leading to the renal carcinogenic findings in the male rat are largely known and strongly indicate that the nephropathy associated with male rats have no significance for human risk assessment [Burdock *et al.*, 1990].

Based on the results of these subchronic and chronic studies, it can be concluded that the renal pathology reported in male rats treated with the linear and branched-chain aliphatic and alicyclic ketones in the KB4/KB3 mixtures is unrelated to the human health assessment. It can also be concluded that exposure to low levels of the ketones in KB4/KB3 provide no significant potential for toxicity, neurotoxicity or carcinogenicity. Therefore, it is not necessary to conduct additional studies on constituents of the KB4/KB3 mixtures.

3.4.4 Reproductive Toxicity

In two separate OECD 421 reproductive/developmental screening studies (see developmental section below), groups of male or female Sprague-Dawley rats were exposed to atmospheres containing 0, 80, 400, or 1,000 ppm 2-heptanone or 1, 2.5 or 5.0

mg/L (214, 535, or 1070 ppm) of 5-methyl-2-hexanone 6 hours daily for either 50 or 34-47 days, respectively. In addition to measurement of maternal and reproductive parameters, epididymal spermatozoan numbers, sperm motility and testicular spermatid head counts were monitored. Male and females were evaluated for clinical signs, body weight gain and food consumption. Measurement of reproductive parameters revealed no evidence of reproductive toxicity even at the highest exposure level for either substance. Based on a decrease in body weight in the 2-heptanone study, the maternal NOAEL was concluded to be 80 ppm [Eastman Kodak Co., 1996, 2001b]. When these data are combined with the observation that there were no effects to reproductive organs in the subchronic or chronic studies on linear and branched-chain aliphatic and alicyclic ketones (see repeat dose studies) it is concluded that the aliphatic ketones in KB4 exhibit a low potential for reproductive toxicity.

In a screening assay for fertility activity, groups of 8 female CF1 mice were given 50 mg/kg bw dose of 2-pentadecanone, 8-pentadecanone, or 2-undecanone by intraperitioneal injection daily during gestation. Diethylstilbesterol was administered as a positive control (10 ug/kg bw). Dams were observed for signs of toxicity and body weights were recorded during gestation. The percent pregnant, number of viable fetuses per litter, number of resorption sites, and dead in utero per litter were recorded and expressed as a percent of the control value. No effects on maternal body weight were observed and no sign of toxicity were reported. For the test groups compared to the control group, pregnancy rate was in the range of 50-100%, the average number of resortion sites per litter was 0% and the average number of fetuses per litter was in the range of 60-81%. Diethylstilbesterol was used as a positive control (10 ug/kg bw). The positive control showed 0% pregnancy rate, 0% fetuses per litter, and 0% resorption sites per litter. Under conditions of the experiment, a 50 mg/kg bw dose of 8- or 2-pentadecanone or 2-undecanone given daily by intraperitoneal injection to female rats produced no maternal and no or mild reproductive effects [Carlson *et al.*, 1975].

Virgin Crl CD rats were administered oral dose levels of 0, 150, 750, or 1,500 mg/kg bw/day of a mixture of alkyl-substituted cyclohexanones and cyclohexanols used in the 28-day study above [Serota, 1990] by gavage for 7 days prior to cohabitation, through

cohabitation (maximum of 7 days), gestation, delivery, and a 4-day post-parturition period. The duration of the study was 39 days [Hoberman, 1989]. The composition of the test material was identical to that used in the 28-day study [Vollmuth, 1990, no robust summary provided]. The study design included measurement of parameters for reproductive and developmental toxicity. Maternal indices monitored included twice-daily clinical observation, measurement of body weights, food consumption, duration of gestation, and fertility parameters (mating and fertility index, gestation index, and number of offspring per litter). Offspring indices monitored included daily observation, clinical signs, examination for gross external malformations, and measurement of mortality (number of stillborns), viability (pups dying on days 1-4), body weight and body weight gain.

At the two highest dose levels, maternal mortality was increased, significant decreases in maternal body weight and food consumption were reported, clinical observations of the dams included decreased motor activity, ataxia, dysnea, rales, chromorrhinorrhea, un-groomed coat and thin appearance, and significant increases in pup mortality were reported. Live litters were reported for 9/19, 8/10, 5/6, and 1/4 pregnant females in the control, 150, 750, and 1,500 mg/kg bw/day groups, respectively. Increased number of dams with stillborn pups, stillborn pups, and late resorptions *in utero* were reported in the mid-dose group. At the highest dose, 2 rats had only resorptions *in utero* when found dead on gestation day 23 and one rat possessed only empty implantation sites *in utero* on day 25 of presumed gestation. Even at the highest dose level, there was no evidence of an effect of the test article on implantation, duration of gestation, pup sex ratio, or gross morphology of pups. Based on these results the authors concluded that the maternal NOAEL for reproductive effects was 150 mg/kg bw/day and the offspring NOAEL for developmental effects is greater than 150 mg/kg bw/day, but less than 750 mg/kg bw/day.

In a dominant lethal assay, males rats were gavaged with up to 3,000 mg/kg bw of 2-isopropyl-5-methylcyclohexanol as a single exposure or up to 1,150 mg/kg bw/day of 2-isopropyl-5-methylcyclohexanol for 5 days [Food and Drug Administration, 1975]. Male rats were mated with 2 female rats per week for 7-8 weeks following the last treatment. Fourteen days after mating, females were killed and the uterus was examined for early

deaths, late fetal deaths, and total implantations. No effect on early deaths, late fetal deaths and total implantations was reported when 2-isopropyl-5-methylcyclohexanol was administered to male rats prior to mating.

Given the lack of any significant reproductive effects in the reproductive/developmental screening studies and the absence of any significant effects to the reproductive organs of animals in subchronic and chronic repeat dose studies, it is concluded that aliphatic ketones and alkyl-substituted cyclohexanones exhibits a very low order of reproductive toxicity. No additional testing is recommended for the KB4/KB3 mixture.

3.4.5 Developmental Toxicity

Groups of pregnant LAK:LVG(SYR) hamsters were given 0, 96, or 960 mg/kg bw of 6,10-dimethyl-2-undecatrienone dissolved in acetone (5%) and solubilized in Tween 20 by gavage on day 8 of pregnancy. The low- mid-, and high-dose group contained 6, 9, and 14 animals. The doses were chosen based on the median effective dose of retinoids that induce terata (ED50) in hamsters. Animals were sacrificed on Day 14 and average fetal and maternal body weights were measured. Developmental parameters monitored included, number of litters, abnormal litters, implantation sites, number of resorptions, number of abnormal live fetuses, number dead fetuses, mean litter frequency, and characterization of malformations. The only effect reported was a significant reduction in maternal weight gain in the 960 mg/kg bw group. The authors concluded that dose levels up to and including 960 mg/kg bw failed to show any evidence of developmental toxicity in golden Syrian hamsters. Based on the depressed body weights of females at 960 mg/kg, the dose level of 96 mg/kg was concluded to be the NOAEL for maternal toxicity [Willhite, 1986].

Two OECD 421 reproductive/developmental screening studies have been performed on a straight-chain (2-heptanone) and a branched-chain (5-methyl-2-hexanone) ketone. Groups of male or female Sprague-Dawley rats were exposed to atmospheres containing 0, 80, 400, or 1000 ppm 2-heptanone 6 hours daily for either 50 or 34-47 days, respectively. Male and females were monitored for clinical signs, body weight gain and

food consumption. All adult animals survived to study termination and there were no test substance-related changes in mean terminal body weight. For the 1000 ppm male group, there was a reduction in food consumption during days 0-7. Otherwise, there were no other differences in mean body weight, body weight gain, food consumption or food utilization among the groups throughout the study. Except for minimal reductions in activity level observed in the 400 and 1000 ppm groups during each exposure, no other test substance-related clinical abnormalities were noted. Mean sperm motility and mean epididymal spermatozoan and testicular spermatid counts were comparable among test and control groups. No test substance-related gross pathology was observed for adult animals from any group. No exposure-related changes were observed during histological examination of the reproductive organs of any of the test groups. There were no changes in pup clinical signs or body weight of the test groups compared to the controls. There were no abnormalities of the skeletal or tissues that could be related to administration of the test substance. Based on these data the no observable adverse effect concentration (NOAEC) for parental toxicity was concluded to be 80 ppm and the NOAEC for fetotoxicity was concluded to be 1000 ppm, the highest concentration tested [Eastman Kodak Co., 1996].

In the second study, groups of Sprague Dawley rats were exposed to 0, 1.0, 2.5, or 5.0 mg/L of 5-methyl-2-hexanone for 51(males) or 35-41 days (females). There was no evidence of parental, reproductive or fetal toxicity at any dose level tested. The NOEC for either toxicity endpoint exceeded 5.0 mg/L [Eastman Kodak Co., 2001b].

In an inhalation teratology study, groups of female Fischer F344 rats and CD-1 mice (22/group) were exposed to atmospheres containing 0, 25, 50, or 110 ppm of 3,5,5-trimethyl-2-cyclohexenone 6 hours daily during days 6 to 15 of gestation. There were no significant changes in the clinical signs, body weights, food consumption, or gross evaluation at necropsy for the test and control groups of dams of either species. Measurement of live and dead fetuses and number of early and late resorptions and evaluation of implantation sites and Corpora lutea revealed no significant differences between test and control groups. There were no skeletal malformations or ossification variations that were considered related to exposure to the test substance for either species.

The NOEC for Fisher F344 female rats and CD-1 female mice was reported to be 1,150 ppm [Traul, 1984].

Based on the interconvertability of alicyclic/aliphatic ketones and alcohols *in vivo*, data on the corresponding alcohol is also considered relevant to the teratogenic potential of the corresponding ketone. Teratology studies in four animal species were performed under Food and Drug Administration contracts for the isomer of 2-isopropyl-5-methylcyclohexanol. Studies in mice [Morgareidge, 1973a], rats [Morgareidge, 1973b], and hamsters [Morgareidge, 1973c] were performed using the same study design. In each study, virgin adult females (CD-1 outbred mice, Wistar rats, or golden hamsters) were mated with untreated young adult males and observation of vaginal sperm plugs was considered day 0 of gestation. Beginning on day 6 and continuing daily through day 15 (mice and rats) or day 10 (for hamsters) of gestation, groups (22-23 for mice, 22-25 for rats and 19 to 23 for hamsters) of pregnant females were given 2-isopropyl-5-methylcyclohexanol by gavage in corn oil. Mice received 0, 1.85, 8.59, 39.9, or 185 mg/kg bw/day, rats received 2.18, 10.15, 47.05, or 218 mg/kg bw/day, and hamsters received 0.05, 21.15, 98.2, or 405 mg/kg bw/day. Negative control groups received corn oil by gavage daily while positive control groups received aspirin. On day 17(mice), 20 (rats), or 14 (hamsters), all dams were subjected to Caesarian section and the number of live litters, implantation sites, number of resorptions, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, implant sites per dam, percent of live and percent partial live resorptions, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. One-third of fetuses of each litter underwent detailed visceral examination at 10 times magnification. The remaining two-thirds were stained with alizarin red S dye/KOH and examined for skeletal defects. No effects on these parameters were reported in any of the species tested and the authors concluded that there was no evidence of maternal or developmental toxicity at dose levels up to and including 185 (mice), 218 (rats), and 405 (hamsters) mg/kg bw/day of 2-isopropyl-5-methylcyclohexanol during gestation.

Virgin adult female rabbits were artificially inseminated and beginning on gestation day 6 and continuing daily through day 18, pregnant rabbits were given 0, 4.25, 19.75, 91.7, or 425 mg/kg bw of 2-isopropyl-5-methylcyclohexanol by gavage in corn oil [Morgareidge, 1973d]. A positive control group received 2.5 mg/kg bw/day of 6-aminonicotinamide. On gestation day 29 all dams were subjected to Caesarian section and the number of *corpora lutea*, implantation sites, resorption sites, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were recorded. The urogenital tract of each dam was examined for anatomical abnormalities. All live fetuses were placed in an incubator for 24 hours and evaluated for survival. All surviving pups were sacrificed and subjected to detailed visceral examination at 10 times magnification. All fetuses were cleared with KOH, stained with alizarin red S dye, and examined for skeletal defects. As reported for the 3 other species, there was no evidence of either maternal toxicity or developmental toxicity at dose levels up to and including 425 mg/kg bw/day of 2-isopropyl-5-methylcyclohexanol. Given the results of this multiple species study, alkyl-substituted cyclohexanol derivatives exhibit a low potential for developmental toxicity.

In summary, the developmental toxicity testing for three aliphatic linear or branched-chain ketones and for two cyclohexanone derivatives indicated that constituents of the KB4/KB3 mixtures exhibit a low potential for developmental toxicity.

3.4.6 New Testing Required

No further testing is required.

4 REFERENCES FOR TEST PLAN AND ROBUST SUMMARIES

Abbott P.J. (2000) Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups. Safety Evaluation of certain food additives and contaminants. International Programme on Chemical Safety, World Health Organization, Geneva. **44**, 229-260.

Abraham M. H. (1994) KOWWIN EPI Suite (2000) US Environmental Protection Agency.

Alarie Y. *et al.* (1995) MPBPVPWIN EPI Suite (2000) US Environmental Protection Agency.

AOPWIN EPI Suite (2000) U S Environmental Protection Agency.

Asakawa Y., Ishida, T., Toyota, M. and Takemoto T. (1986) Terpenoid transformation in mammals IV. Biotransformation of (+)-longifolene, (-)-caryophyllene, (-)-caryophyllene oxide, (-)-cyclocolorenone, (+)-nootkatone, (-)-elemol, (-)-abietic acid, and (+)-dehydroabietic acid in rabbits. *Xenobiotica* **16**, 753-767.

Atzl G., Bertl M., Daxenbichler G. and Gleispach H. (1972) Determination of etheral oils from the urine by gas-liquid chromatography. *Chromatographia* **5**, 250-255.

BASF (1974) Acute toxicity studies on 6-methyl-5-hepten-2-one. Unpublished report.

BIOWIN EPI Suite (2000) US Environmental Protection Agency.

Bonte W., Rudell E., Sprung R., Frauenrath C., Blanke E., Kupilas G., Wochinik J., and Zah G. (1981) Experimental investigations concerning the blood-analytical detection of small doses of higher aliphatic alcohols in man. *J. Blutalkohol*, **18**, 399-411.

Borghoff S.J., Short B.G. and Swenberg J.A. (1990) Biochemical mechanisms and pathobiology of nephropathy. *Annual Reveiws of Pharmacology and Toxicology* **30,** 349-367.

Bringmann G. and Kuehn, R. (1977) efunde der Schadwirkung wassergefaehrdender Stoffe gegen Daphnia magna. [Results of the damaging effects of water pollutants on *Daphnia magna*.] *A Wasser Abwasser Forsch.*, **10(5),** 161-166.

Broderius S. and Kahl M. (1985) Acute toxicity of organic chemical mixtures to the fathead minnow. *Aquatic Toxicology,* **6,** 307-322.

Buccafusco R.J., Ells S.J., and LeBlanc G. A. (1981) Acute toxicity of priority pollutants to Bluegill. *Bulletin of Environmental Contaminant Toxicology,* **26**, 446-452.

Bucher J.R., Huff J., and Kluwe W.M. (1986) Toxicology and carcinogenesis studies of isophorone in F344 rats and B6C3F1 mice. *Toxicology,* **39(2),** 207-219.

Burdock G. A., Wagner B. M., Smith R. L., Munro I. C. and Newberne P. M. (1990) Recent progress in the consideration of flavoring ingredients under the food additives amendment. 15. GRAS Substances. *Food Technology* **44,** 78-86.

Carlson G. L., Hall I. H., and Piantadosi (1975) Cycloalkanone. 7. Hypocholesterolemic acitivity of aliphatic compounds related to 2,8-dibenzylcyclooctanone. Journal of Medicinal Chemistry 18(10), 234-236.

Cheo K.L., Elliott T. H. and Tao R. C. C. (1967) The metabolism of the isomeric tert-butylcyclohexanones. *Biochem. J*. **104**, 198-204.

CIVO-TNO (1999) Volatile Components in Food-Qualitative and Quantitative Data. Supplement 5 to the 6th Edition. Edited by H. Maarse, C.A. Visscher, L.C. Willemsens, L.M. Nijssen, and M.H. Boelens. TNO Nutrition and Food Research. Zeist, The Netherlands.

Clayton J. D. and Clayton F. E. (1994) Patty's Industrial Hygiene and Toxicology., 4th Ed., Ketones. Eds Topping C. D., Morgott D. a., David R. M., and O'Donoghue J. L., pp 1749-1750.

Conkle J.P., Camp, B.J., and Welch, B.E. (1975) Trace composition of human respiratory gas. *Archs Envir. Hlth*, **30**, 290-295.

CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

Cuervo A.M. Hildebrand H., Bomhard E.M. and Dice J.F. (1999) Direct lysosomal uptake of *alpha*-2-microglobulin contributes to chemically induced nephropathy. *Kidney International* **55(2),** 529-545.

Deichmann W. and Thomas G. (1943) Glucuronic acid in the urine as a measure of the absorption of certain organic compounds. *Journal of Industrial Hygiene and Toxicology,* **25**, 286-292.

Dietrich D.R. and Swenberg J.A. (1991) NCI-Reiter (NBR) male rats fail to develop renal disease following exposure to agents that induce α-2μ-globulin ($\alpha_{2\mu}$) nephropathy. *Fundamental and Applied Toxicology* **16**, 749-762.

Dietz F.K., Rodriguez-Giaxola, M., Traiger, G.J., Stella, V.J., and Himmelstein, K.J. (1981) Pharmacokinetics of 2-butanol and its metabolites in the rat. J. Pharmacokinet. Biopharm., **9,** 553-576.

Dragoco Gerberding and Co. GmbH (2000) Acute toxicity study of 2-tridecanone by oral administration to Sprague-Dawley rats. Unpublished report.

Dutertre-Catella H., Nguyen P., Dang Q. and Truhaut R. (1978) Metabolic transformations of the trimethyl-3,5,5, cyclohexene-2, one-1 (isophorone). *Toxicological European Research* **1,** 209-216.

Eastman Chemical Co. (1997a) Chemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services division, Eastman Kodak Company, Rochester, NY; Report No. COD-00590. July 24, 1997.

Eastman Chemical Co. (1997b) Biochemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00589. July 24, 1997.

Eastman Kodak Co. (2001a) A growth inhibition test with alga, Selenastrum capricornutum. Enviromental Sciences Section, Health and Environment Laboratories, Eastman Kodak Co., Rochester, NY.

Eastman Kodak Co. (2001b) Reproduction/Developmental toxicity screening test in the rat. Toxicological Sciences Laboratory, Health and Environment Laboratories. Study No. HAEL 2000-0208. Laboratory Project ID 2000208I1.

Eastman Kodak Co. (2000) An acute aquatic effects test with the Daphnid (*daphna magna*); Environmental Sciences Section, Health and Environment Laboratories, HAEL No. 78-0260.

Eastman Kodak Co. (1998) A growth inhibition test with alga, *Selenastrum capricornutum*. Enviromental Sciences Section, Health and Environment Laboratories, Eastman Kodak Co., Rochester, NY.

Eastman Kodak Co. (1996) Reproduction/Developmental toxicity screening test in the rat. Toxicological Sciences Laboratory, Health and Environment Laboratories. Study No. HAEL 95-0202.

Eastman Kodak Co. (1979) 90-day repeated oral administration of five ketones and n-heptane to rats. Unpublished report.

Eastman Kodak Co. (1978) An acute aquatic effects test with the Fathead Minnow (Pimephales promelas);Environmental Sciences Section, Health and Environment Laboratories, HAEL No. 78-0260.

ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Eisenberg F., Field J. B. and Stetten D. (1955) Studies on glucuronide conjugation in man. *Archives of Biochemistry and Biophysics* **59**, 297-299.

Elliott T.H., Parke D.V. and Williams R.T. (1959) Studies in detoxication. The metabolism of cyclo[^{14}C]hexane and its derivatives. *Biochemistry Journal* **72,** 193-200.

Elliott T.H., Tao R. C. C. and Williams R.T. (1965) Studies in detoxication. The metabolism of isomeric methylcyclohexanones. *Biochemistry Journal* **95,** 59-65.

Engineering Sciences Unit (1975) MPBPVP EPI Suite (2000) US Environmental Protection Agency.

Environmental Protection Agency (EPA) (1991) Risk assessment forum. *alpha*-2 micro-globulin: association with chemically induced renal toxicity and neoplasia in the male rat. Publication no. EPA/625/3-91019F.

Exxon Chemical Americas (1982) Unpublished report to Environmental Protection Agency.

Felsted R. L. and Bachur, N. R. (1980) Ketone Reductases. In Enzymatic Basis Of Detoxification. Edited by W.B. Jacoby. Volume I. pp. 281-293. Academic Press, New York.

Florin, I., Rutberg, L., Curvall, M. and Enzell, C. R. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology **18,** 219-232.

Fragrance Materials Association (FMA) Private communication. Unpublished report.

Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

Foureman P., Mason J.M., Valencia R. and Zimmering S. (1994) Chemical Mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environmental and Molecular Mutagenesis* **23**, 208-227.

Gabriel M.A., Ilbawi M. and Al-Khalidi U.A.S. (1972) The oxidation of acetoin to CO2 in intact animals and in liver mince preparation. *Comp. Biochem. Physiol.* **41B**, 493-502.

Geiger D.L., Poirer S.H., Brooke L. T. and Call D.J., eds (1986) Acute toxicities of organic chemicals to fathead minnows (Pimephales Promelas). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior. Unpublished report.

Governa M., Calisti R., Coppa G., Tagliavento G., Colombi A. and Troni W. (1987) Urinary excretion of 2,5-hexanedione and peripheral polyneuropathies in workers exposed to hexane. *Journal of Toxicology and Environmental Health* **20,** 219.

Gry J. (1999) Saturated aliphatic acyclic secondary alcohols, ketones and related saturated and unsaturated esters. Safety Evaluation of certain food additives and contaminants. International Programme on Chemical Safety, World Organization, Geneva. 42: 235-265.

Hall R.L. and Oser, B. L. (1965) Recent progress in the consideration of flavoring ingredients under the food additives amendment. III GRAS Substances. *Food Technology*, **19**, 151-197.

Hansch C., Quinlan J. E., and Lawrence G. L. (1967) The linear free-energy relationship between partition coefficients and aqueous solubility of organic liquids. *Journal of Oraganic Chemistry*, **33**, 347-351.

Hansch C. and Leo A. (1979).Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York, 339p.

Hansch C., Kim D., Leo A. J., Novellino E., Silipo C., and Vittoria A. (1989) Toward a comparative toxicology of organic compounds. Critical Reviews in Toxicology, 19, 185-226.

Hildebrand H., Hartmann E., Popp A., and Bomhard E. (1997) Quantitation of a_2-microglobulin after administration of structurally divergent chemical compounds. *Archives of Toxicology* **71,** 351-359.

Hoberman A. M. (1989) Reproductive and developmental toxicity screening of B100 administeredorally via gavage to Crl:CD(SD)Br female rats. Argus Research Laboratories, Inc. Protocol 412-015. Private Communication to FEMA. Unpublished report.

Hoffman-LaRoche (1967) Acute toxicity, eye, and skin irritation tests of fragrance materials. Unpublished report to RIFM.

Homan E.R., and Maronpot, R.R. (1978) Neurotoxic evaluation of some aliphatic ketones. *Toxicology and Applied Pharmacology*, **45**, 312.

James S.P. and Waring R.H. (1971) The metabolism of alicyclic ketones in the rabbit and rat. *Xenobiotica* **1**, 573-580.

JECFA (1999) Saturated aliphatic acyclic secondary alcohols, ketones, and related saturated and unsaturated esters. In Safety Evaluation of Certain Food Additives and Contaminants. International Programme on Chemical Safety, World Health Organization., Geneva, Vol. 42, pp. 235-265.

JECFA (2003) Alicyclic Ketones, Secondary Alcohols and Related Esters. In Press. International Programme on Chemical Safety, World Health Organization, Geneva.

Kaffenberger R.M. and Doyle M.J. (1990) Determination of menthol and menthol glucuronide in human urine by gas chromatography using an enzyme-sensitive internal standard and flame ionization detection. *Journal of Chromatography* **527**, 59-66.

Kamil A.I., Smith, J.N., and Williams, R.T. (1953) The metabolism of aliphatic alcohols; the glucuronic acid conjugation of acyclic aliphatic alcohols. *J. Biochemistry*, **53**, 129-136.

Kasper C.B. and Henton D. (1982) Glucuronidation. In *Enzymatic Basis of Detoxification*. Edited by W. B. Jakoby. 2: 4-36. Academic Press, New York.

Katz G.V., O'Donoghue, J.L., DiVincenzo, G.D., and Terhaar, C.J. (1980) Comparative neurotoxicity and metabolism ethyl n-butyl ketone and methyl n-butyl ketone in rats. *Toxicol. Appl. Pharmacol*., **52**, 153-158

Keating J. (1972) Acute oral toxicity in rats, dermal toxicity in rabbits. Unpublished report to RIFM dated June 7, 1972.

Kjeldsen L., Cowland J.B. and Borregaard N. (2000) Human neutrophil gelatinase-associated lipocalin and homologous proteins in rat and mouse. *Biochimica Biophysica Acta* **1482**(1-2), 272-283.

Klimisch H. J., Andreae, M. and U. Tillman (1997) A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Journal of Regulatory Toxicology and Pharmacology,* **25**, 1-5.

Koeferl M.T., Miller T.R., Fisher J.D., Martis L., Garvin P.J. and Dorner J.L. (1981) Influence of concentration and rate of intravenous administration on the toxicity of cyclohexanone in beagle dogs. *Toxicology and Applied Pharmacology* **59**, 215-229.

KOWWIN EPI Suite (2000) US Environmental Protection Agency.

Krasavage W.J., O'Donoghue, J.L., DiVincenzo, G.D., and Terhaar, C.J. (1980) The relative neurotoxicity of methyl-n-butyl ketone, n-hexane and their metabolites. *Toxicol. Appl. Pharmacol*. **53**, 433-441.

Krasavage W.J., and O'Donoghue, J.L. (1979) Repeated oral administration of five ketones and n-heptane to rats. Unpublished report.

Lehman A.J., Schwerma, H., and Rickards, E. (1945) Isopropyl alcohol: Acquired tolerance in dogs, rate of disappearance from the blood stream in various species, and effects on successive generation of rats. *J. Pharmacol. Exp. Therap*., **85(1)**, 61-69.

Lehman-McKeeman L.D. and Caudill D. (1999) Development of an *in vitro* competitive binding assay to predict *alpha*-2 micro-globulin nephropathy. *In Vitro and Molecular Toxicology* **12**(2), 83-95.

Lehman-McKeeman L.D. and Caudill D. (1994) *d*-Limonene induced hyaline droplet nephropathy in *alpha*-2 micro-globulin transgenic mice. *Fundamental and Applied Toxicology* **23,** 562-568.

Lehman-McKeeman L.D. and Caudill D. (1992) Biochemical Basis for Mouse Resistance to Hyaline Droplet Nephropathy: Lack of relevance to the *alpha*-2 micro-globulin protein superfamily in this male rat-specific syndrome. *Toxicology and Applied Pharmacology* **112**, 214-221.

Lehman-McKeeman L.D., Rodriguez P.A, Takigiku R., Caudill D. and Fey M.L. (1989) *d*-Limonene-induced male rat-specific Nephrotoxicity: evaluation of the assosciation

between d-limonene and *alpha*-2 micro-globulin. *Toxicology and Applied Pharmacology* **99**, 250-259.

Levenstein I. (1974) Acute toxicity study in rats and rabbits. Unpublished report to RIFM.

Lington A.W. and Bevan C. (1994) Alcohols in Patty's Industrial Hygiene and Toxicology, 4th ed. Edited by Clayton and Clayton, Volume IID pp.2585-2760. John Wiley & Sons, Inc., New York.

Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183.

Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. *Environmental Toxicology and Chemistry*, **15(9),** 1618-1626.

Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. *Environmental Toxicology and Chemistry*, **15(9),** 1627-1637.

Madyastha K.M. and Srivatsan. (1988) Studies on the metabolism of l-menthol in rats. *Metabolism and Disposition* **16**, 765.

Martis L., Tolhurst T, Koeferl M.T., Miller T.R. and Darby T.D. (1980) Disposition Kinetics of cyclohexanone in beagle dogs. *Toxicology and Applied Pharmacology* **59**(2), 215-229.

Moreno O. (1980) Acute Toxicity Studies. Project No. MB80-4817A. Unpublished report to RIFM.

Morgareidge K. (1973a) Teratologic evaluation of FDA 71-57 in mice. Contract No. FDA 71-260. Unpulished report.

Morgareidge K. (1973b) Teratologic evaluation of FDA 71-57 in rats. Contract No. FDA 71-260. Unpulished report.

Morgareidge K. (1973c) Teratologic evaluation of FDA 71-57 in hamsters. Contract No. FDA 71-260. Unpulished report.

Morgareidge K. (1973d) Teratologic evaluation of FDA 71-57 in rabbits. Contract No. FDA 71-260. Unpulished report.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B and Zeiger, E. (1986) Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. *Environmental Mutagenesis* **8(Supplement 7),** 1-119.

MPBPVPWIN EPI Suite (2000) US Environmental Protection Agency.

Mraz J., Galova E., Nohova H. and Vitkova D. (1994) Uptake, metabolism and elimination of cyclohexanone in humans. *International Archives of Occupational and Environmental Health.* **66**(3), 203-208.

National Cancer Institute (NCI) (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.

National Toxicology Program (NTP) (1990) Toxicology and carcinogenesis studies of d-limonene in F344/N rats and B6C3F1 mice (gavage studies). NTP-TR-347; NIH Publication No. 88-2902. National Institute of Environmental Health Sciences, National Institute of Health, Public Health Service, Department of Health and Human Services, Research Triangle Park, NC.

National Toxicology Program (NTP) (1986) Toxicology and carcinogenesis studies of isophorone in F344/N rats and B6C3F1 mice (gavage studies). NTP-TR-291; NIH Publication No. 86- 2547. National Institute of Environmental Health Sciences, National Institute of Health, Public Health Service, Department of Health and Human Services, Research Triangle Park, NC.

Nelson S. D., McClanahan R. H., Thomassen D., Gordon W. P. and Knebel N. (1992) Investigations of mechanisms of reactive metabolite formation from (R)-(+)-pulegone. *Xenobiotica* **22**, 1157-1164.

Nordmann R., Ribiere C., Rouach H., Beauge F., Giudicelli Y. and Nordmann J. (1973) Metabolic pathways involved in the oxidation of isopropanol into acetone by the intact rat. *Life Science*, **13**, 919-932.

O'Donoghue J.L., Haworth S.R., Curren R.D., Kirby P.E., Lawlor T., Moran E.J., Phillips R.D., Putnam D.L., Rogers-Back A.M., Slesinski R.S., and Thilagar A. (1988) Mutagenicity studies on ketone solvents: Methyl ethyl ketone, methyl isobutyl ketone, and isophorone. *Mutation Research*, **206**, 149-161.

O'Donoghue J.L., Krasavage, W.J., DiVincenzo, G.D., and Katz, G.V. (1984) Further studies on ketone neurotoxicity and interactions. *Toxiclogy and Applied Pharmacology*, **72**, 201-209.

O'Donohogue J. L. and Krasavage W. J., DiVencenzo G. and Ziegler D.(1982) Commercial grade methyl heptyl ketone (5-methyl-2-octanone) neurotoxicity: Contribution of 5-nonanone.*Toxiclogy and Applied Pharmacology*, **62**, 307-316.

O'Donohogue J. L. and Krasavage W. J. (1980) 90-Day repeated oral administration of five keones and n-heptane to rats. Private communication to FEMA. Unpublished report.

Ohe S. (1976) MPBPVP EPI Suite (2000) US Environmental Protection Agency.

Olson M.J., Johnson J.T. and Reidy C.A. (1990) A comparison of male rat and human urinary proteins: implications for human resistance to hyaline droplet nephropathy. *Toxicology and Applied Pharmacology* **102,** 524-536.

Palit S. R. (1947) *Journal of Physical Chemistry*, **51,** 827.

Perbellini L., Brugnone F. and Pavan I (1980) Identificatio of the metabolites of n-Hexane, cyclohexane and their isomers in men's urine. *Toxicology and Applied Pharmacology* **53**, 220-229.

Perry R. H. and Green D (1984) MPBPVPWIN EPI Suite (2000) US Environmental Protection Agency.

Quick A.J. (1924) The synthesis of menthol glucuronide acid in the rabbit. *Journal of Biological Chemistry* **61**, 679-683.

Quick A.J. (1928) Quantitative studies of *beta*-oxidation. IV. The metabolism of conjugated glycuronic acids. *Journal of Biological Chemistry* **80**, 535-541.

Roy A. K. and Neuhaus, O.W. (1967) Androgenic control of a sex dependent protein in rat. *Nature* **214,** 618-620.S

Saito K., Uwagawa S., Kaneko H., Shiba K., Tomigahara Y. and Nakatsuka I. (1996) *alpha*-2 micro-globulin in the urine of male rats: a reliable indicator for *alpha*-2 micro-globulin accumulation in the kidney. *Toxicology*. **106,** 149-157.

Sakata M, Kikuchi J. and Haga M. (1989) Disposition of acetone, methyl ethyl ketone and cyclohexanone in acute poisoning. *Clinical Toxicology* **27**(1-2), 67-77.

Schultz T.W. (1997) TETRATOX: Tetrahymena pyriformis population growth impairment endpoint-asurrogate for fish lethality. *Toxicology Methods*, **7**, 289-309.

Schultz T.W. Wyatt N.L., Lin D.T. (1990) Structure-toxicity of nonpolar narcotics: A comparison of data from the Tetrahymen, Photobacterium and Pimephales systems.

Serota D. G. (1990) 28-Day oral toxicity study in rats: B100. HLA Study No. 642-477. Private Communication to FEMA. Unpublished report.

Shelby M.D., Erexson, G.L., Hook, G.J., and Tice, R.R. (1993) Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. *Environ Mol Mutagen* **21**,160-179.

Springborn Labortories (2001) Ready Biodegradability by the closed bottle method. Study No. 1852.6173.

Stofberg J. and F. Grundschober (1987) The consumption ratio and Food Predominance of flavoring materials. *Perfumer & Flavorist*, **12**, 27-56.

Stofberg J. and J. C. Kirschman (1985) The consumption ratio of flavoring materials: A mechanism for setting priorities for safety evaluation. *Food and Chemical Toxicology,* **23**, 857-860.

Strasser J., Jr., Charbonneau M., Borghoff S.J., Turner M.J. and Swenberg J.A. (1988) Renal protein droplet formation in male Fischer 344 rats after isophorone (IPH) treatment. *Toxicologist* **8**, 136.

Swenberg J. A., Short B., Borghoff S., Strasser J. and Charbonneau M. (1989) The comparative pathobiology of nephropathy. *Toxicology and Applied Pharmacology* **97**, 35-46.

Syracuse Research Corporation (SRC) Private communication to Fragrance Materials Association (FMA).

Tanii H., Tsuji, H., Hashimoto, K. (1986) Structure -Toxicity Relationship of Monoketones. *Toxicology Letters*, **30(1),** 13-17.

Tao C.C. and Elliott T.H. (1962) The metabolism of 14C-methylcyclohexane. *Journal of Biochemistry,* **84,** 38-39.

Topping D.C, Morgott, D.A., David R.M. and O'Donoghue J.L. (1994) Ketones in *Patty's Industrial Hygiene and Toxicology, 4th ed.* Edited by Clayton and Clayton, Volume IIC pp.1739-1878. John Wiley & Sons, Inc., New York.

Traul K.A. (1984) Inhalation teratology study in mice and rats. Biodynamics Inc. Project No. 323772. Unpublished report.

Treon J.F., Crutchfield W.E., Jr. and Kitzmiller K.V. (1943a) he physiological response of rabbits to cyclohexane, methylcyclohexane, and certain derivatives of these compounds. I. Oral administration and cutaneous application. *Journal of Industrial Hygiene and Toxicology* **25(6),** 199-214.

Treon J.F., Crutchfield W.E., Jr. and Kitzmiller K.V. (1943b) The physiological response of animals to cyclohexane, methylcyclohexane, and certain derivatives of these compounds. II. Inhalation. *Journal of Industrial Hygiene and Toxicology*, **25(8),** 323-347**.**

Triebel S., Blaser J., Reinke H. and Tschesche H. (1992) A 25 kDa *alpha*-2-microglobulin-related protein is a component of the 125 kDa form of gelatinase. *FEBS Letters* **314**(3), 386-388.

Truhaut R., Dutertre-Catella H. and Nguyen P. (1970) Metabolic study of an industrial solvent, isophorone, in the rabbit. *Comptes rendus hebdomadaires des seances de l'Academie des sciences. Serie D: Sciences naturelles.* **271,** 1333-1336.

Untermann R.D., Lynch K.R., Nakhasi H.L., Dolan K.P., Hamilton J.W., Cohn D.V. and Feigelson P. (1981) Cloning and sequencing of several *alpha*-2-microglobulin cDNAs. *Proceedings of the National Academy of Science*, **78,** 3478-3482.

Van Miller J.P. and Gill M. W. (1987) 14-day dietary minimum toxicity screen of 4-(2-furyl)-3-buten-2-one, oxotetradecanoic acid glyceride, 3-oxooctanoic acid glyceride, 2-pentadecanone, and o-methoxybenzaldehyde. Report to FEMA. Unpublished.

Veith G., Call, D., Brooke, L. (1983) Structure -Toxicity Relationships for Fathead Minnow (Pimephales promelas) Narcotic industrial chemicals. *Canadian Journal of Fish. Aqua. Sci.*, **40**, 743-748.

Vollmuth T. A. (1989) Stability Profile of B100/450 – dosing solution. Private Communication to FEMA. Unpublished report

Wallington T. J. and Kurylo, M. J. (1987) Flash photolysis resonance fluorescence investigation of the gas-phase reaction of OH radicals with a series of aliphatic ketones over the temperature range 240-444 K. *Journal of Chemical Physics*, **91,** 5050-5054.

Wang K.S. and Hodgetts, R.B. (1998) The analysis of regulatory sequences required for the high level induction of rat *alpha*-2–µ-globulin gene expression by dexamethasone. *Journal of Molecular Endocrinology* **20**(1), 129-139.

Webb D.R., Kanerva, R.L., Hysell, D.K., Alden, C.L. and Lehman-McKeeman, L.D. (1990) Assessment of the subchronic oral toxicity of *d*-limonene in dogs. *Food and Chemical Toxicology **28,*** 669-675.

Wild D., King, M.-T., Gocke, E. and Eckhardt, K. (1983). Study of Artifical Flavouring Susbtances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. *Fd. Chem. Toxic.*, **21(6),** 707-719.

Willhite C. C. (1986) Structure-activity relationships of retenoids in developmental toxicology. II Influence of polyene chain of the Vitamin A molecule. *Toxicology and Applied pharmacology*, **83**, 563-575.

Williams R.T. (1939) Studies in Detoxication. III. The use of the glucuronic acid detoxication mechanism of the rabbit for the resolution of dl-menthol. *Biochemical Journal* **33**, 1519-1524.

Williams R. T. (1940) Studies in detoxication. 7. The biological reduction of l-Menthone to d-neomenthol and of d-isomenthone to d-isomenthol in the rabbit. The conjugation of d-neomenthol with glucuronic acid. *Biochemical Journal* **34**, 690-697.

Wouters M.F.A. and Speijers G.J.A. (1999) Safety Evaluation of aliphatic acyclic and alicyclic ? ?diketones and related ? -hydroxyketones. Safety Evaluation of certain

food additives and contaminants. International Programme on Chemical Safety, World Health Organization, Geneva. 42, 353-379.

WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

Yamaguchi T., Caldwell J. and Farmer P.B. (1994) Metabolic fate of [3H]-l-menthol in the rat. *Drug Metabolism and Disposition* **22**, 616-624.

Zlatkis A., Poole, C.F., Brazeli, R., and Bafus, D.A. (1980) Volatile metabolites in sera of normal and diabetic patients. *J. Chromatogr*. **182**, 137-145.

201-15014B

Robust Summaries for Ketone Bottoms (KB4/KB3)

Ketone Bottoms (KB4/KB3)

CAS No. 68990-20-5

Eastman Chemical Company

Registration Number

Submitted to the EPA under the HPV Challenge Program by:

Eastman Chemical Company
100 North Eastman Road
Kingsport, TN 37662
Phone: 423-229-5208
Fax: 423-224-0208

Table of Contents

Robust Summaries for Ketone Bottoms (KB4/KB3)

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al*., 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 CHEMICAL AND PHYSICAL PROPERTIES

1.1 Melting Point

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Melting Point	-8 °C
Decomposition	
Sublimation	
Remarks for Results	

Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.
CAS	925-78-0
Substance Name	3-Nonanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Melting Point	-18.94 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Syracuse Research Corporation (SRC) Private communication to FMA.
CAS	4485-09-0
Substance Name	4-Nonanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	

Melting Point	-5.85 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	502-56-7
Substance Name	5-Nonanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1976
Remarks for Test Conditions	
Melting Point	-5.9 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Alarie Y. *et al*. (1995) MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	502-56-7
Substance Name	5-Nonanone
Remarks for substance	
Method/guideline	Experimental

GLP	Ambiguous
Year	1994
Remarks for Test Conditions	
Melting Point	-4.8 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Clayton J. D. and Clayton F. E. (1994) Patty's Industrial Hygiene and Toxicology, 4th Ed., Ketones. Eds Topping C. D., Morgott D. a., David R. M., and O'Donoghue J. L., pp 1749-1750.

CAS	693-54-9
Substance Name	2-Decanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Melting Point	14 °C; freezing point 3.1 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	928-80-3
Substance Name	3-Decanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Melting Point	2.5 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	928-80-3
Substance Name	3-Decanone
Remarks for substance	Same predicted data for 2-, 4-, or 5-decanone.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Melting Point	5.92 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	624-16-8
Substance Name	4-Decanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Melting Point	-9 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1984
Remarks for Test Conditions	
Melting Point	15 °C
Decomposition	

Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Perry R. H. and Green D (1984) MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Melting Point	12.1 - 12.7 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for substance	
Method/guideline	Calculated
GLP	

Year	
Remarks for Test Conditions	
Melting Point	10 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	2216-87-7
Substance Name	3-Undecanone
Remarks for substance	Same predicted data for 2-, 4-, 5-, or 6-undecanone
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Melting Point	17.15 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	14476-37-0
Substance Name	4-Undecanone

Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Melting Point	4.5 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	927-49-1
Substance Name	6-Undecanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Melting Point	15 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc.,

	Boca Raton, FL.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1984
Remarks for Test Conditions	
Melting Point	21 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Perry R. H. and Green D (1984) MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for substance	Same predicted data for 3-, 4-, 5-, or 6-dodecanone
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Melting Point	27.86 °C
Decomposition	
Sublimation	
Remarks for Results	

Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	1534-27-6
Substance Name	3-Dodecanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Melting Point	19 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.
CAS	6137-26-4
Substance Name	4-Dodecanone
Remarks for substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Melting Point	10 °C

Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Melting Point	-1.09 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for substance	Same predicted data for 2,6- or 2,4-dimethylcyclohexanone
Method/guideline	Calculated
GLP	

Year	
Remarks for Test Conditions	
Melting Point	-13.73 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for substance	Data for isomer, 5-methyl-3-heptanone isomer
Method/guideline	Experimental
GLP	Ambiguous
Year	1994
Remarks for Test Conditions	
Melting Point	-56.7 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Clayton J. D. and Clayton F. E. (1994) Patty's Industrial Hygiene and Toxicology, 4th Ed., Ketones. Eds Topping C. D., Morgott D. a., David R. M., and O'Donoghue J. L., pp 1749-1750.
CAS Numerical	2345-28-0

Substance Name	2-Pentadecanone
Remarks for substance	
Method/guideline	Experimental
GLP	
Year	
Remarks for Test Conditions	
Melting Point	39.5 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS Numerical	2345-28-0
Substance Name	2-Pentadecanone
Remarks for substance	Same predicted data for 2-, 6-, 8-pentadecanone
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Melting Point	46.2 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS Numerical	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Melting Point	-7.03 °C
Decomposition	
Sublimation	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS Numerical	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Melting Point	9.03 °C
Decomposition	
Sublimation	
Remarks for Results	

Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

1.2 Boiling Point

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	195.3 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	821-55-6
Substance Name	2-Nonanone

Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Boiling Point	192 °C
Pressure	742 mm Hg
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Fragrance Materials Association (FMA) Private communication.

CAS	925-78-0
Substance Name	3-Nonanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Boiling Point	187 °C
Pressure	751 mm
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report

	which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.
CAS	925-78-0
Substance Name	3-Nonanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Boiling Point	190 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Fragrance Materials Association (FMA) Private communication.
CAS	4485-09-0
Substance Name	4-Nonanone
Remarks for Substance	Same predicted data for 2-, 3-, 4-, 5-nonanone.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	184.65 °C
Pressure	

Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	502-56-7
Substance Name	5-Nonanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1994
Remarks for Test Conditions	
Boiling Point	188.4 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Clayton J. D. and Clayton F. E. (1994) Patty's Industrial Hygiene and Toxicology, 4th Ed., Ketones. Eds Topping C. D., Morgott D. A., David R. M., and O'Donoghue J. L., pp 1749-1750.
CAS	502-56-7
Substance Name	5-Nonanone
Remarks for Substance	

Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	186-187 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	211; 215.5 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.

References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.
CAS	928-80-3
Substance Name	3-Decanone
Remarks for Substance	Same predicted data for 2-, 3-, 4-, 5-decanone.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	204.79 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	624-16-8
Substance Name	4-Decanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	206 - 207 °C
Pressure	
Pressure Unit	

Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	228 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	
Method/guideline	Experimental

GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	231 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Fragrance Materials Association (FMA) Private communication.

CAS	2216-87-7
Substance Name	3-Undecanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Boiling Point	227 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	2216-87-7
Substance Name	3-Undecanone
Remarks for Substance	Same predicted data for 2-, 3-, 4-, 5-, 6-undecanone.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	224.03 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	927-49-1
Substance Name	6-Undecanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	228 °C (corr.)
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	

Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.
CAS	1534-27-6
Substance Name	3-Dodecanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	234 °C
Pressure	18 mm Hg
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1984

Remarks for Test Conditions	
Boiling Point	246.5 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Perry R. H. and Green D. (1984) MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Same predicted data for 2-, 3-, 4-, 5-, 6-dodecanone.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	242.37 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	2979-19-3

Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	179 °C
Pressure	748 mmHg
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	178-179 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	174 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	823-55-2
Substance Name	2,4-Dimethylcyclohexanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	

Boiling Point	171 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	
Method/guideline	Experimental
GLP	Ambiguous
Year	1960
Remarks for Test Conditions	
Boiling Point	171 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

CAS	2345-28-0

Substance Name	2-Pentadecanone
Remarks for Substance	
Method/guideline	Experimental
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	294 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Same predicted data for 2-, 6-, 8-pentadecanone
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	291.95 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for Substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	212.54 °C
Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for Substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Boiling Point	224.46 °C

Pressure	
Pressure Unit	
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

1.3 Vapor Pressure

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Vapor Pressure	0.30 mm Hg
Temperature	20 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Fragrance Materials Association (FMA) Private communication. Unpublished report.

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	1976
Remarks for Test Conditions	
Vapor Pressure	0.642 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Ohe S. (1976) MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	820-29-1
Substance Name	2-Nonanone
Remarks for substance	Calculated vapor pressure values for 2-,3-, 4-, or 5-nonanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	0.933 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	925-78-0
Substance Name	3-Nonanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	
Remarks for Test Conditions	
Vapor Pressure	0.83 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Syracuse Research Corporation (SRC)
CAS	502-56-7
Substance Name	5-Nonanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	1995
Remarks for Test Conditions	
Vapor Pressure	0.552 mm Hg
Temperature	25 °C

Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Alarie Y. *et al*. (1995) MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	1995
Remarks for Test Conditions	
Vapor Pressure	0.269 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Perry R. H. and Green D (1984) MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for substance	Calculated vapor pressure values for 2-, 3-, 4-, or 5-decanone are equivalent.
Method/guideline	Calculated
GLP	

Year	
Remarks for Test Conditions	
Vapor Pressure	0.449 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	1984
Remarks for Test Conditions	
Vapor Pressure	0.0414mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Perry R. H. and Green D (1984) MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone

Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	0.03mm Hg
Temperature	20 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Fragrance Materials Association (FMA) Private communication. Unpublished report.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for substance	Calculated vapor pressure values for 2-, 3-, 4-, 5- or 6-undecanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	0.14mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	927-49-1
Substance Name	6-Undecanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	1975
Remarks for Test Conditions	
Vapor Pressure	0.05 mm Hg
Temperature	20 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Engineering Sciences Unit (1975) MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for substance	
Method/guideline	Measured
GLP	Ambiguous
Year	1984
Remarks for Test Conditions	
Vapor Pressure	0.0206 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Perry R. H. and Green D (1984) MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	1534-27-6
Substance Name	3-Dodecanone
Remarks for substance	Calculated vapor pressure values for 2-, 3-, 4-, or 5-dodecanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	0.065 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	1.32 mm Hg
Temperature	25 °C

Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	1.04 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	

Remarks for Test Conditions	
Vapor Pressure	1.66 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	823-55-2
Substance Name	2,4-Dimethylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	1.04 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.
CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for substance	Calculated vapor pressure values for 2-, 6-, or 8-Pentadecanone are equivalent.

Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	0.0036 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	0.284 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Vapor Pressure	0.158 mm Hg
Temperature	25 °C
Decomposition	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

1.4 n-Octanol/Water Partition Coefficients

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for substance	
Method/guideline	GC method
GLP	
Year	1986
Remarks for Test Conditions	Analysis was carried out using gas chromatograph equipped with flame ionization detector and PEG 20M glass column. Column temperature was 155 C. Volume for partitioning was 8.0 ml water and 0.01 ml octanol. Values are means of triplicate

	runs.
Log Pow	3.14
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Tanii H., Tsuji H., Hashimoto K. (1986) Structure-toxicity relationships of monoketones. Toxicology Letters 30, 13-17.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for substance	Calculated values of log Kow for 2-, 3-, 4-, or 5-nonanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Log Pow	2.71
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	502-56-7
Substance Name	5-Nonanone
Remarks for substance	
Method/guideline	Experimental
GLP	

Year	1989
Remarks for Test Conditions	
Log Pow	3.06
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Hansch C., Kim D., Leo A. J., Novellino E., Silipo C., and Vittoria A. (1989). Toward a comparative toxicology of organic compounds. Critical Reviews in Toxicology 19, 185-226.

CAS	502-56-7
Substance Name	5-Nonanone
Remarks for substance	
Method/guideline	Experimental
GLP	
Year	1967
Remarks for Test Conditions	Partition coefficient was calculated from the molecular fragment constant method.
Log Pow	2.79
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Hansch C., Quinlan J. E., and Lawrence G. L. (1967) The linear free-energy relationship between partition coefficients and aqueous solubility of organic liquids. Journal of Organic Chemistry, 33, 347-351.

CAS	502-56-7
Substance Name	5-Nonanone

Remarks for substance	
Method/guideline	Experimental
GLP	
Year	1994
Remarks for Test Conditions	
Log Pow	2.88
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Abraham M. H. (1994) KOWWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for substance	
Method/guideline	Experimental
GLP	
Year	1989
Remarks for Test Conditions	
Log Pow	3.60
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Hansch C., Kim D., Leo A. J., Novellino E., Silipo C., and Vittoria A. (1989). Toward a comparative toxicology of organic compounds. Critical Reviews in Toxicology 19, 185-226.
CAS	693-54-9

Substance Name	2-Decanone
Remarks for substance	
Method/guideline	GC method
GLP	
Year	1986
Remarks for Test Conditions	Analysis was carried out using gas chromatograph equipped with flame ionization detector and SE 30 glass column. Column temperature was 155 C. Volume for partitioning was 20.0 ml water and 0.03 ml octanol. Values are means of triplicate runs.
Log Pow	3.73
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Tanii H., Tsuji H., Hashimoto K. (1986) Structure-toxicity relationships of monoketones. Toxicology Letters 30, 13-17.

CAS	693-54-9
Substance Name	2-Decanone
Remarks for substance	Calculated values of log Kow for 2-, 3-, 4-, or 5-decanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Log Pow	3.21
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for substance	
Method/guideline	GC method
GLP	
Year	1986
Remarks for Test Conditions	Analysis was carried out using gas chromatograph equipped with flame ionization detector and SE 30 glass column. Column temperature was 170 C. Volume for partitioning was 16.0 ml water and 0.01 ml octanol. Values are means of triplicate runs.
Log Pow	4.09
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Tanii H., Tsuji H., Hashimoto K. (1986) Structure-toxicity relationships of monoketones. Toxicology Letters 30, 13-17.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for substance	Calculated values of log Kow for 2-, 3-, 4-, 5-, or 6-undecanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Log Pow	3.69
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.

Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for substance	Data are for higher homologue, 7-tridecanone
Method/guideline	Experimental
GLP	
Year	1979
Remarks for Test Conditions	Partition coefficient calculated from molecular fragment constant method.
Log Pow	5.17
Temperature	25 °C
Remarks for Results	Partition coefficient of 2-dodecanone estimated to be 4.6
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Hansch C. and Leo A. (1979) Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York, 339p.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for substance	Calculated values of log Kow for 2-, 3-, 4-, 5-, or 6-dodecanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Log Pow	4.18
Temperature	25 °C
Remarks for Results	

Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for substance	Calculated values of log Kow for 3,3- 2,3-, 2,6-, or 2,4-dimethylcyclohexanone are equivalent.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Log Pow	1.98
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for substance	Data for homologue, 2-octanone
Method/guideline	Experimental
GLP	
Year	1989
Remarks for Test Conditions	
Log Pow	2.52
Temperature	25 °C

Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Hansch C., Kim D., Leo A. J., Novellino E., Silipo C., and Vittoria A. (1989) Toward a comparative toxicology of organic compounds. Critical Reviews in Toxicology, 19, 185-226.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for substance	Data for homologue, 2-octanone
Method/guideline	Experimental
GLP	
Year	1979
Remarks for Test Conditions	Partition coefficient calculated from molecular fragment constant method.
Log Pow	2.46
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Hansch C. and Leo A. (1979) Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York, 339p.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	

Remarks for Test Conditions	
Log Pow	2.42
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for substance	Calculated values of log Kow for 2-, 6-, 8-pentadecanone
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Log Pow	5.66
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for substance	
Method/guideline	Calculated
GLP	

Year	
Remarks for Test Conditions	
Log Pow	3.62
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Log Pow	2.94
Temperature	25 °C
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.

1.5 Water Solubility

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data for 2-, 3-, 4-, and 5-nonanone are shown.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	170.6 mg/L for 2-nonanone, 396.1 mg/L for 3-nonanone, 284.4 mg/L for 4- or 5-nonanone
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

CAS	502-56-7
Substance Name	5-Nonanone
Remarks for Substance	
Method/guideline	Experimental
GLP	No
Year	1947
Remarks for Test Conditions	

Value (mg/L) at temperature	376 mg/L at 25 °C
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	Data cited in Hansch *et al.,* 1967
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Palit S. R. (1947) Journal of Physical Chemistry, 51, 827.

CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Data for 2-, 3-, 4-, and 5-decanone are shown.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	46.4 mg/L for 2-decanone, 131 mg/L for 3-, 4- or 5-decanone
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

CAS	112-12-9
Substance Name	2-Undecanone

Remarks for Substance	Data for 2-, 3-, 4-, 5-, and 6-undecanone are shown.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	19.7 mg/L for 2-undecanone, 42.9 mg/L for 3-, 4-, 5-, or 6-undecanone
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Data for 2-, 3-, 4-, 5-, and 6-dodecanone are shown.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	14 mg/L for 2-, 3-, 4-, 5-, or 6-dodecanone
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.

Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	1874 mg/L at 25 °C
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	1371 mg/L at 25 °C
Description of Solubility	

pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Data for 2-, 6-, and 8-Pentadecanone are shown.
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	0.468 mg/L at 25 °C
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for Substance	
Method/guideline	Calculated

GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	49.63 mg/L at 25 °
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for Substance	
Method/guideline	Calculated
GLP	
Year	
Remarks for Test Conditions	
Value (mg/L) at temperature	222.7 mg/L at 25 °C
Description of Solubility	
pH value and concentration at temp	
pKa value at 25 Celsius	
Remarks for Results	
Conclusion Remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

2 ENVIRONMENTAL FATE AND PATHWAYS

2.1 Photodegradation

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Assay: 99%
Method/guideline	Flash photolysis resonance fluorescence
Test Type	Hydroxyl radical reaction
GLP	No
Year	1987
Light Source	Nitrogen-pulsed discharge lamp
Light Spectrum (nm)	165 nm
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	Hydroxyl radicals were produced by ultraviolet flash photolysis of water at 0.1 Torr. Radical concentrations were monitored as a function of time by fluorescence from an OH microwave resonance lamp. Hydroxyl radical concentrations were maintained between 10 exp 10 to 10 exp 11 molecules/cm3. Concentration anticipated to be sufficient to assure pseudo-first order kinetics for radical decay.
Concentration of Substance	
Temperature	296K
Direct photolysis	
Halflife t1/2	6.3 hours at atmospheric
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=122 x 10exp-13 cu cm/molecule.sec

Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	Material is expected to undergo rapid degradation in the atmosphere.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Wallington T. J. and Kurylo, M. J. (1987) Flash photolysis resonance fluorescence investigation of the gas-phase reaction of OH radicals with a series of aliphatic ketones over the temperature range 240-444 K. Journal of Chemical Physics, 91, 5050-5054.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data for 2-, 3-, 4-, and 5-nonanone are shown.
Method/guideline	Calculation
Test Type	AOPWIN
GLP	
Year	2000
Light Source	
Light Spectrum (nm)	
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2=11.67 hrs for 2-nonanone, 11.979 hrs for 3-nonanone, 10.073 hrs for 4-nonanone, and 9.639 hrs for 5-nonanone
Degradation % after	
Quantum yield	
Indirect photolysis	

Sensitizer	
Concentration of sensitizer	
Rate constant	k=10.99 x 10exp-12 cu cm/molecule-sec for 2-nonanone, 10.71 x 10 exp-12 cu cm/molecule-sec for 3-nonanone, 12.74 x 10exp-12 cu cm/molecule-sec for 4-nonanone, 13.311 x 10exp-12 cu cm/molecule-sec for 5-nonanone
Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Assay: 98%
Method/guideline	Flash photolysis resonance fluorescence
Test Type	Hydroxyl radical reaction
GLP	No
Year	1987
Light Source	Nitrogen-pulsed discharge lamp
Light Spectrum (nm)	165 nm
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	Hydroxyl radicals were produced by ultraviolet flash photolysis of water at 0.1 Torr. Radical concentrations were monitored as a function of time by fluorescence from an OH microwave resonance lamp. Hydroxyl radical concentrations were maintained between 10 exp 10 to 10 exp 11 molecules/cm3. Concentration anticipated to be sufficient to assure pseudo-first order kinetics for radical decay.
Concentration of Substance	
Temperature	296K

Direct photolysis	
Halflife t1/2	6.8 hours at atmospheric
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=132 x 10exp-13 cu cm/molecule.sec
Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	Material is expected to undergo rapid degradation in the atmosphere
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Wallington T. J. and Kurylo, M. J. (1987) Flash photolysis resonance fluorescence investigation of the gas-phase reaction of OH radicals with a series of aliphatic ketones over the temperature range 240-444 K. Journal of Chemical Physics, 91, 5050-5054.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Data for 2-, 3-, 4-, and 5-decanone are shown.
Method/guideline	Calculation
Test Type	AOPWIN
GLP	
Year	2000
Light Source	
Light Spectrum (nm)	
Relative Intensity	
Spectrum of Substance	

Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2=10.34 hrs for 2-decanone, 10.58 hrs for 3-decanone, 9.067 hrs for 4-decanone, and 8.714 hrs for 5-decanone
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=12.40 x 10exp-12 cu cm/molecule-sec for 2-decanone, 12.128 x 10 exp-12 cu cm/molecule-sec for 3-decanone, 14.156 x 10exp-12 cu cm/molecule-sec for 4-decanone, 14.73 x 10exp-12 cu cm/molecule-sec for 5-decanone
Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Data for 2-, 3-, 4-, 5-, and 6-undecanone are shown.
Method/guideline	Calculation
Test Type	AOPWIN
GLP	
Year	2000
Light Source	
Light Spectrum (nm)	

Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2=9.28 hrs for 2-undecanone, 9.48 hrs for 3-undecanone, 8.244 hrs for 4-undecanone, and 7.951 hrs for 5- and 6-undecanone
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=13.82 x 10exp-12 cu cm/molecule-sec for 2-undecanone, 13.54 x 10 exp-12 cu cm/molecule-sec for 3-undecanone, 15.568 x 10exp-12 cu cm/molecule-sec for 4-undecanone, 16.14 x 10exp-12 cu cm/molecule-sec for 5- and 6-undecanone
Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Data for 2-, 3-, 4-, 5-, and 6-dodecanone are shown.
Method/guideline	Calculation
Test Type	AOPWIN

GLP	
Year	2000
Light Source	
Light Spectrum (nm)	
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2=8.423 hrs for 2-dodecanone, 8.583 hrs for 3-dodecanone, 7.558 hrs for 4-dodecanone, and 7.31 hrs for 5- and 6-dodecanone
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=15.23 x 10exp-12 cu cm/molecule-sec for 2-dodecanone, 14.95 x 10 exp-12 cu cm/molecule-sec for 3-dodecanone, 16.98 x 10exp-12 cu cm/molecule-sec for 4-dodecanone, 17.55 x 10exp-12 cu cm/molecule-sec for 5- and 6-dodecanone
Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	2979-19-3

Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data for 3,3-, 2,3-, 2,6-, and 2,4-dimethylcyclohexanone are shown.
Method/guideline	Calculation
Test Type	AOPWIN
GLP	
Year	2000
Light Source	
Light Spectrum (nm)	
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2=16.142 hrs for 3,3-isomer, 6.921 hrs for 2,3- isomer, 8.549 hrs for 2,6- isomer, and 8.419 hrs for 2,4- isomer
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=9.7512 x 10exp-12 cu cm/molecule-sec for 3,3- isomer, 18.548 x10 exp-12 cu cm/molecule-sec for 2,3-isomer, 15.014 x 10exp-12 cu cm/molecule-sec for 2,6-isomer, and 15.248 x 10exp-12 cu cm/molecule-sec for 2,4-isomer
Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Assay: 99%. Data are for isomer 2-octanone.
Method/guideline	Flash photolysis resonance fluorescence
Test Type	Hydroxyl radical reaction
GLP	No
Year	1987
Light Source	Nitrogen-pulsed discharge lamp
Light Spectrum (nm)	165 nm
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	Hydroxyl radicals were produced by ultraviolet flash photolysis of water at 0.1 Torr. Radical concentrations were monitored as a function of time by fluorescence from an OH microwave resonance lamp. Hydroxyl radical concentrations were maintained between 10 exp 10 to 10 exp 11 molecules/cm3. Concentration anticipated to be sufficient to assure pseudo-first order kinetics for radical decay.
Concentration of Substance	
Temperature	296K
Direct photolysis	
Halflife t1/2	5.8 hours at atmospheric
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=110 x 10exp-13 cu cm/molecule.sec
Degradation %after	
Breakdown products	
Remarks field for results	
Conclusion remarks	Material is expected to undergo rapid degradation in the atmosphere

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Wallington T. J. and Kurylo, M. J. (1987) Flash photolysis resonance fluorescence investigation of the gas-phase reaction of OH radicals with a series of aliphatic ketones over the temperature range 240-444 K. Journal of Chemical Physics, 91, 5050-5054.
CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for Substance	
Method/guideline	Calculation
Test Type	AOPWIN
GLP	
Year	2000
Light Source	
Light Spectrum (nm)	
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2 = 8.844 hours
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=1.4512 x 10exp-12 cu cm/molecule-sec
Degradation %after	
Breakdown products	

Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for Substance	
Method/guideline	Calculation
Test Type	AOPWIN
GLP	
Year	2000
Light Source	
Light Spectrum (nm)	
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2 = 4.792 hours
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=26.7 x 10exp-12 cu cm/molecule-sec
Degradation %after	
Breakdown products	

Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Data for 2-, 6- and 8- 2-Pentadecone are shown.
Method/guideline	Calculation
Test Type	AOPWIN
GLP	
Year	2000
Light Source	
Light Spectrum (nm)	
Relative Intensity	
Spectrum of Substance	
Remarks for Test Conditions	
Concentration of Substance	
Temperature	
Direct photolysis	
Halflife t1/2	t1/2 = 6.590 hours
Degradation % after	
Quantum yield	
Indirect photolysis	
Sensitizer	
Concentration of sensitizer	
Rate constant	k=19.478 x 10exp-12 cu cm/molecule-sec
Degradation %after	
Breakdown products	

Remarks field for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.

2.2 Biodegradation

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data are for homologue, 2-heptanone; purity 99.7%
Method	Method C.5.: "Degradation, Biochemical Oxygen Demand" Method is similar to OECD: TG-301C: Modified MITI Test.
Test Type	Biochemical Oxygen Demand (BOD)
GLP	Yes
Year	1997
Contact time (units)	
Innoculum	
Remarks for Test Conditions	BOD was determined after 5 and 20 days. The 20-day value was performed in duplicate. The microbial innoculum was prepared from a mixed liquor seed water sample obtained from Kings Landing water treatment facility. The concentration of the innoculum for the study was prepared a 100 ml of the seed water to 2 liters of distilled water. The initial concentration of the test substance was 1 ml of test substance to 1 liter or reagent water.
Degradation % after time	
Results	BOD was 1.77 g BOD/g of test substance BOD20 was 2.00 g BOD/g of test substance
Kinetic	
Time required for 10% degradation	

10 day window criteria	
Total degradation	
Classification	Readily biodegradable
Breakdown products (transient or stable)	
Remarks fields for results	The BOD 20 value was a mean of two replicates.
Conclusion remarks	The substance is considered to be "Readily Biodegradable" based on a BOD5/COD ratio greater than 0.5 (1.77/2.42 = 0.73).
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Eastman Chemical Co. (1997b) Biochemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00589. July 24, 1997.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data are for homologue, 2-heptanone; purity 99.7%.
Method	Method C.6, Degradation, Chemical Oxygen Demand, Official Journal of European Communities, No. 383A/227, 9/12/92
Test Type	Chemical Oxygen Demand (COD)
GLP	Yes
Year	1997
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	2.42 g COD/g of test substance
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	Readily biodegradable

Breakdown products (transient or stable)	
Remarks fields for results	The value is a mean of three replicates.
Conclusion remarks	The substance is concluded to be readily biodegradable based on COD criteria.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Eastman Chemical Co. (1997a) Chemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services division, Eastman Kodak Company, Rochester, NY; Report No. COD-00590. July 24, 1997.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	The model predictions for 2-, 3-, 4-, or 5-nonanone are similar.
Method	Calculated
Test Type	
GLP	
Year	
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks and days to weeks, respectively.
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	

Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	The model predictions for 2-, 3-, 4-, or 5-decanone are similar.
Method	Calculated
Test Type	
GLP	
Year	
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks and days to weeks, respectively.
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	
Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	The model predictions for 2-, 3-, 4-, 5-, or 6-undecanone are similar.
Method	Calculated
Test Type	
GLP	
Year	
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks and days to weeks, respectively.
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	
Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	The model predictions for 2-, 3-, 4-, 5-, or 6-dodecanone are

	similar.
Method	Calculated
Test Type	
GLP	
Year	
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks and days to weeks, respectively.
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	
Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	The model predictions for 2,3-, 3,3-, 2,4-, or 2, 6-dimethylcyclohexanone are similar.
Method	Calculated
Test Type	
GLP	

Year	
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks to months and weeks, respectively.
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	
Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for structurally related substance 5-methyl-2-hexanone, purity 99.3%.
Method	OECD TG-301D
Test Type	Ready Biodegradability by the Closed Bottle Method
GLP	Yes
Year	2001
Contact time (units)	28 days
Innoculum	Activated sludge
Remarks for Test Conditions	Benzoic acid at 10 mg/L was used as a reference control. The test material was assessed at a nominal concentration of 2.5

	mg/L. Test vessels of 300 ml BOD bottles were prepared per treatment (reference, test substance and innoculum blank), two each for Day 0 and three per sampling interval (Day 7, 14, 21, 28). After the bottles were filled they were closed and wrapped in tin foil.
Degradation % after time	67% (greater than 60% by Day 14)
Results	
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	Readily biodegradable
Breakdown products (transient or stable)	
Remarks fields for results	Benzoic acid reference was degraded 72%. The temperature of the environment ranged from 20-22 deg C. Dissolved oxygen concentrations in the control blank ranged from 8.7 mg/L on Day 0 to 7.1 mg/L on Day 28. The protocol stated that oxygen depletion in the controls should not exceed a loss of 1.5 mg/L before Day 28; however, the loss was 1.6 mg/L. This protocol deviation was viewed as minor and does not affect the overall conclusion as it occurred well after Day 14 when the material had already met the readily biodegradable pass level of greater than 60%.
Conclusion remarks	Material is considered readily biodegradable under the conditions of this test.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Springborn Laboratories (2001) Ready Biodegradability by the closed bottle method. Study No. 1852.6173.
CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for Substance	
Method	Calculated
Test Type	
GLP	
Year	

Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks to months and weeks, respectively
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	
Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for Substance	
Method	Calculated
Test Type	
GLP	
Year	
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	

Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks to months and weeks, respectively.
Kinetic	
Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	
Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.
CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	The model predictions for 2-, 6-, and 8-Pentadecanone are similar.
Method	Calculated
Test Type	
GLP	
Year	
Contact time (units)	
Innoculum	
Remarks for Test Conditions	
Degradation % after time	
Results	MITI Nonlinear Biodegradation Probability Model predicts that the substance is readily biodegradable. The Survey Model predicts ultimate and primary biodegradability within weeks to months and weeks, respectively.
Kinetic	

Time required for 10% degradation	
10 day window criteria	
Total degradation	
Classification	
Breakdown products (transient or stable)	
Remarks fields for results	
Conclusion remarks	The substance is concluded to be readily biodegradable.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

2.3 Fugacity

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data for 2-, 3-, 4-, and 5-nonanone are shown.
Model Conditions	
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	

Volatility

Model data and results	Half-lives, t(1/2): Air = 19.3 to 24 hrs for all isomeric nonanones Water = 360 hrs for all isomeric nonanones Soil = 360 hrs for all isomeric nonanones Sediment = 1.44 x 10(+3) hrs for all isomeric nonanones
Estimated Distribution and Media Concentration	Air = 4.31% for 2-, 5.08% for 3-, 4.21% for 4-, and 5.675% for 5-nonanone Water = 30.5% for 2-, 32.7% for 3-, 32.0 for 4-, and 36.3% for 5-nonanone Soil = 64.8% for 2-, 62.0% for 3-, 63.5% for 4-, and 57.8% for 5-nonanone Sediment = 0.407% for 2-, 0.23
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Data for 2-, 3-, 4-, and 5-decanone are shown.
Model Conditions	
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	

absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 17.4 to 21.3 hrs for all isomeric decanones Water = 360 hrs for all isomeric decanones Soil = 360 hrs for all isomeric decanones Sediment = 1.44 x 10(+3) hrs for all isomeric decanones
Estimated Distribution and Media Concentration	Air = 3.90% for 2-, 4.42% for 3-, 3.94% for 4-, and 5.38% for 5-decanone Water = 28.8% for 2-, 29.9% for 3-, 30.1% for 4-, and 34.9% for 5-decanone Soil = 66.2% for 2-, 65.2% for 3-, 65.6% for 4-, and 59.4% for 5-decanone Sediment = 1.09% for 2-, 0.44
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Data for 2-, 3-, 4-, 5-, and 6-undecanone are shown
Model Conditions	
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000

Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 15.9 to 19.3 hrs for all isomeric undecanones Water = 208-360 hrs for all isomeric undecanones Soil = 208-360 hrs for all isomeric undecanones Sediment = 832-1440 hrs for all isomeric undecanones
Estimated Distribution and Media Concentration	Air = 2.81% for 2-, 4.00% for 3-, 3.15% for 4-, 4.48% for 5- and 6-undecanone Water = 33.9% for 2-, 28.2% for 3-, 30.9% for 4-, and 35.9% for 5- and 6-undecanone Soil = 60.6% for 2-, 66.8% for 3-, 64.9% for 4-, and 58.9% for 5- and 6-undecanone Sediment
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Data for 2-, 3-, 4-, 5-, and 6-dodecanone are shown
Model Conditions	
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model

Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 14.6 to 17.2 hrs for all isomeric dodecanones Water = 208-360 hrs for all isomeric dodecanones Soil = 208-360 hrs for all isomeric dodecanones Sediment = 832-1440 hrs for all isomeric dodecanones
Estimated Distribution and Media Concentration	Air = 3.60% for 2-, 3.65% for 3-, 3.31% for 4-, 4.68% for 5-dodecanone Water = 26.7% for 2-, 26.7% for 3-, 26.8% for 4-, and 32.5% for 5-dodecanone Soil = 67.1% for 2-, 67.1% for 3-, 76.3% for 4-, and 61.0% for 5-dodecanone Sediment = 2.54% for 2-, 2.
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data for 2,3-, 3,3-, 2,4-, and 2,6-dimethylcyclohexanones are shown
Model Conditions	
Test Type	Environmental Equilibrium Partitioning Model

Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 13.8 to 32.3 hrs for all isomeric dimethylcyclohexanones Water = 360-900 hrs for all isomeric dimethylcyclohexanones Soil = 360-900 hrs for all isomeric dimethylcyclohexanones Sediment = 1440-3600 hrs for all isomeric dime
Estimated Distribution and Media Concentration	Air = 2.62% for 3,3-, 2.59% for 2,3-, 3.02% for 2,4-, 3.24% for 2,6-dimethylcyclohexanones Water = 37.9% for 3,3-, 42.3% for 2,3-, 42.1% for 2,4-, 41.8% for 2,6-dimethylcyclohexanones Soil = 59.3% for 3,3-, 55.0% for 2,3-, 54.7% for 2,4-, 54.9% for 2,6-
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	
Model Conditions	

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 28.6 hr Water = 360 hr Soil = 360 hr Sediment = 1440 hr
Estimated Distribution and Media Concentration	Air = 6.6% Water = 38.15% Soil = 55.2% Sediment = 0.133%
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for Substance	
Model Conditions	

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 17.7 hrs Water = 360 hrs Soil = 360 hrs Sediment = 1440 hrs
Estimated Distribution and Media Concentration	Air = 3.91% Water = 28.1% Soil = 67.1% Sediment = 0.86%
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for Substance	
Model Conditions	

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 9.58 hrs Water = 360 hrs Soil = 360 hrs Sediment = 1440 hrs
Estimated Distribution and Media Concentration	Air = 1.77% Water = 35.9% Soil = 62.0% Sediment = 6.353%
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.
CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Data for 2-, 6-, and 8-Pentadecanone are shown.
Model Conditions	

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used (title, version, date)	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Remarks for Test Conditions	
Media	
absorption coefficient	
Desorption	
Volatility	
Model data and results	Half-lives, t(1/2): Air = 13.2 hrs Water = 360 hrs Soil = 360 hrs Sediment = 1440 hrs
Estimated Distribution and Media Concentration	Air = 1.93% Water = 16.3% Soil = 48.1% Sediment = 33.7%
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183. Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

3 ECOTOXICITY

3.1 Acute Toxicity to Fish

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Assay: 99+%
Method/guideline	96-hr LC50
Test Type	Flow-through
GLP	Yes
Year	1980
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Fathead minnows, 31 days of age and of mean length 21.0 mm, were treated with nominal concentrations of 0, 7.67, 11.8, 18.1, 27.8, or 42.8 mg/L of 2-nonanone in a flow through system at 25 C. The loading rate per tank was 2.76 g/L. Fish were maintained on 16 hours of light and 8 hours of darkness during the test. Fish were not fed 24 hours prior to and during the test. Tank concentrations of the test agent were monitored daily by GLC. Water quality was monitored for dissolved oxygen (6.6 mg/L), hardness (46.6 mg/L CaCO3), alkalinity (45.9 mg/L CaCO3), pH (7.60), and temperature (25.2 C). Experiments at each concentration were performed in duplicate. LC50 and EC50 values were calculated using corrected average tank concentrations and the Trimmed Spearman-Karber method.
Observations on precipitation	
Nominal concentrations as mg/L	0, 7.67, 11.8, 18.1, 27.8, or 42.8 mg/L
Measured concentrations as mg/L	1, 4.23, 7.77, 12.2, 20.4, or 29.9 mg/L
Unit	mg/L
Endpoint value	96-hr LC50 = 15.2 mg/L and. EC50=15.2 mg/L.
Reference substances (if used)	

Remarks fields for results	Affected fish lost schooling behavior, swam near tank bottom, and were hypoactive. Fish were darkly colored, had increased respiration, and lost equilibrium prior to death. Mortalities at 96 hrs: 27.8 mg/L 20/20; 42.8 mg/L, 20/20. No mortalities at lower concentrations.
Conclusion remarks	The LC50 of 2-nonanone in fathead minnows in a flow-through system is reported to be 15.2mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Geiger D.L., Poirer S.H., Brooke L. T. and Call D.J., eds (1986) Acute toxicities of organic chemicals to fathead minnows (Pimephales Promelas). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior. Unpublished Report.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, and 5-nonanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	
Analytical monitoring	
Exposure period (unit)	96 hour
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 22.68 mg/L
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	502-56-7
Substance Name	5-Nonanone
Remarks for Substance	
Method/guideline	96-hr LC50
Test Type	
GLP	No
Year	1983
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Groups of twenty to twenty-five 30 day old fish were maintained at five different concentrations in flow-through systems for 96 hours in Lake Superior water. Deaths were recorded at 1, 3, 6, 12, 24, 48,72, and 96 hours. Concentrations of test substance were measured daily by CG analysis. Water analyses: 24-26 C, hardness = 45.5 mg/L CaCO3, alkalinity = 42.2 mg/L CaCO3, dissolved oxygen maintained at greater than 60% of saturation, pH= 7.5, 20-25 fish per dose, age= 30 day, weight = approximately 0.12 g.
Observations on precipitation	
Nominal concentrations as mg/L	Not given
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 31 mg/L
Reference substances (if used)	
Remarks fields for results	Substance was one of a series of 12 aliphatic ketones tested for acute toxicity in fathead minnows.
Conclusion remarks	The acute 96-hour LC50 of 5-nonanone is 31 mg/L at 25+/-1C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Veith, G., Call, D., Brooke, L. (1983) Structure -Toxicity Relationships for Fathead Minnow (Pimephales promelas) Narcotic industrial chemicals. Canadian Journal of Fish. Aqua. Sci., 40, 743-748.
CAS	502-56-7
Substance Name	5-Nonanone
Remarks for Substance	Assay: 98%
Method/guideline	96-hr LC50
Test Type	Flow-through
GLP	Yes
Year	1980
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Fathead minnows, 30 days of age and of mean length 19.5 mm, were treated with nominal concentrations of 0, 13.5, 22.5, 37.6, or 62.6 mg/L of 5-nonanone in a flow through system at 25 C. The loading rate per tank was 0.464 g/L. Fish were maintained on 16 hours of light and 8 hours of darkness during the test. Fish were not fed 24 hours prior to and during the test. Tank concentrations of the test agent were monitored daily by GLC. Water quality was monitored for dissolved oxygen (7.0 mg/L), hardness (44.5 mg/L CaCO3), alkalinity (43.2 mg/L CaCO3), pH (7.75), and temperature (25.2 C). Experiments at each concentration were performed in duplicate. LC50 and EC50 values were calculated using corrected average tank concentrations and the Trimmed Spearman-Karber method.
Observations on precipitation	
Nominal concentrations as mg/L	0, 13.5, 22.5, 37.6, or 62.6 mg/L
Measured concentrations as mg/L	1, 5.2, 9.7, 16.1, 28, or 40.6 mg/L
Unit	mg/L
Endpoint value	96-hr LC50 = 31 mg/L (95% CI, 29.4-32.6 mg/L). EC50=31.0 mg/L (95% CI, 29.4-32.6 mg/L).
Reference substances (if used)	
Remarks fields for results	Affected fish became hypoactive, lost the schooling ability and equilibrium prior to death. Mortalities at 96 hrs: 37.6 mg/L 4/25

	and 5/25; 62.6mg/L, 25/25 and 25/25. No mortalities at lower concentrations.
Conclusion remarks	The LC50 of 5-nonanone in fathead minnows in a flow-through system is reported to be 31.0 mg/L.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Geiger D.L., Poirer S.H., Brooke L. T. and Call D.J., eds (1986) Acute toxicities of organic chemicals to fathead minnows (Pimephales Promelas). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior. Unpublished Report.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	
Method/guideline	96-hr LC50
Test Type	
GLP	No
Year	1983
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Groups of twenty to twenty-five 30 day old fish were maintained at five different concentrations in flow-through systems for 96 hours in Lake Superior water. Deaths were recorded at 1, 3, 6, 12, 24,48, 72, and 96 hours. Concentrations of test substance were measured daily by CG analysis. Water analyses: 24-26 C, hardness = 45.5 mg/L CaCO3, alkalinity = 42.2 mg/L CaCO3, dissolved oxygen maintained at greater than 60% of saturation, pH= 7.5, 20-25 fish per dose, age= 30 day, weight = approximately 0.12 g.
Observations on precipitation	
Nominal concentrations as mg/L	Not given
Measured concentrations as mg/L	
Unit	
Endpoint value	Acute 96-hr LC50 = 5.7 mg/L
Reference substances (if	

used)	
Remarks fields for results	Substance was one of a series of 12 aliphatic ketones tested for acute toxicity in fathead minnows.
Conclusion remarks	The acute 96-hour LC50 of 2-decanone is 5.7 mg/L at 25+/-1C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Veith, G., Call, D., Brooke, L. (1983) Structure -Toxicity Relationships for Fathead Minnow (Pimephales promelas) Narcotic industrial chemicals. Canadian Journal of Fish. Aqua. Sci., 40, 743-748.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Assay: 95%
Method/guideline	96-hr LC50
Test Type	Flow-through
GLP	Yes
Year	1980
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Fathead minnows, 29 days of age and of mean length 18 mm, were treated with nominal concentrations of 0, 1.7, 2.9, 4.8, 7.9, or 13.2 mg/L of 2-decanone in a flow through system at 25 C. The loading rate per tank was 0.341 g/L. Fish were maintained on 16 hours of light and 8 hours of darkness during the test. Fish were not fed 24 hours prior to and during the test. Tank concentrations of the test agent were monitored daily by GLC. Water quality was monitored for dissolved oxygen (7.4 mg/L), hardness (41.7 mg/L CaCO3), alkalinity (43.0 mg/L CaCO3), pH (7.45), and temperature (24.7 C). Experiments at each concentration were performed in duplicate. LC50 and EC50 values were calculated using corrected average tank concentrations and the Trimmed Spearman-Karber method.
Observations on precipitation	
Nominal concentrations as mg/L	0, 1.7, 2.9, 4.8, 7.9, or 13.2 mg/L
Measured concentrations as mg/L	0, 0.5, 1.2, 2.4, 3.8, or 8.5 mg/L

Unit	mg/L
Endpoint value	96-hr LC50 = 5.7 mg/L(95% CI, 5.4-6.0 mg/L). EC50=5.7 mg/L (95% CI, 5.4-6.0 mg/L).
Reference substances (if used)	
Remarks fields for results	Affected fish became hypoactive, lost the schooling ability and equilibrium prior to death. Mortalities at 96 hrs: 7.9 mg/L 3/25 and 1/25; 13.2 mg/L, 25/25 and 25/25. No mortalities at lower concentrations.
Conclusion remarks	The LC50 of 2-decanone in fathead minnows in a flow-through system is reported to be 5.7 mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Geiger D.L., Poirer S.H., Brooke L. T. and Call D.J., eds (1986) Acute toxicities of organic chemicals to fathead minnows (Pimephales Promelas). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior. Unpublished Report.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, and 5-decanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	
Analytical monitoring	
Exposure period (unit)	96 hour
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 8.627 mg/L

Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Assay: 95%
Method/guideline	96-hr LC50
Test Type	Flow-through
GLP	Yes
Year	1980
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Fathead minnows, 31 days of age and of mean length 21.9 mm, were treated with nominal concentrations of 0, 1.07, 1.64, 2.52, 3.87, or 5.95 mg/L of 2-undecanone in a flow through system at 25 C. The loading rate per tank was 3.14 g/L. Fish were maintained on 16 hours of light and 8 hours of darkness during the test. Fish were not fed 24 hours prior to and during the test. Tank concentrations of the test agent were monitored daily by GLC. Water quality was monitored for dissolved oxygen (6.6 mg/L), hardness (48.8 mg/L CaCO3), alkalinity (45.4 mg/L CaCO3), pH (7.67), and temperature (25.1 C). Experiments at each concentration were performed in duplicate. LC50 and EC50 values were calculated using corrected average tank concentrations and the Trimmed Spearman-Karber method.
Observations on precipitation	
Nominal concentrations as mg/L	0, 1.07, 1.64, 2.52, 3.87, or 5.95 mg/L
Measured concentrations as mg/L	0.16, 0.42, 0.61, 1.04, 1.87, or 3.24 mg/L
Unit	mg/L

Endpoint value	96-hr LC50 = 1.50 mg/L (95% CI, 1.39-1.62 mg/L) and. EC50=1.50 mg/L (95% CI, 1.39-1.62 mg/L)
Reference substances (if used)	
Remarks fields for results	Affected fish lost schooling behavior, swam near tank bottom, and were hypoactive. Fish were darkly colored, had increased respiration, and lost equilibrium prior to death. Mortalities at 96 hrs: 3.87 mg/L 18/20; 5.95 mg/L, 20/20. No mortalities at lower concentrations.
Conclusion remarks	The LC50 of 2-undecanone in fathead minnows in a flow-through system is reported to be 1.50mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Geiger D.L., Poirer S.H., Brooke L. T. and Call D.J., eds (1986) Acute toxicities of organic chemicals to fathead minnows (Pimephales Promelas). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior. Unpublished Report.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, 5-, and 6-undecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	
Analytical monitoring	
Exposure period (unit)	96 hour
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 3.255 mg/L

Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Assay: 99%
Method/guideline	96-hr LC50
Test Type	Flow-through
GLP	Yes
Year	1980
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Fathead minnows, 33 days of age and of mean length 18.3 mm, were treated with nominal concentrations of 0, 0.90, 1.38, 2.12, 3.26, or 5.01 mg/L of 2-dodecanone in a flow through system at 24.8C. The loading rate per tank was 1.76 g/L. Fish were maintained on 16 hours of light and 8 hours of darkness during the test. Fish were not fed 24 hours prior to and during the test. Tank concentrations of the test agent were monitored daily by GLC. Water quality was monitored for dissolved oxygen (6.8 mg/L), hardness (44.4 mg/L CaCO3), alkalinity (44.6 mg/L CaCO3), pH (7.6), and temperature (24.8 C). Experiments at each concentration were performed in duplicate. LC50 and EC50 values were calculated using corrected average tank concentrations and the Trimmed Spearman-Karber method.
Observations on precipitation	
Nominal concentrations as mg/L	0, 0.90, 1.38, 2.12, 3.26, or 5.01 mg/L
Measured concentrations as mg/L	0.10, 0.36, 0.59, 0.71, 1.14, or 2.61 mg/L
Unit	mg/L

Endpoint value	96-hr LC50 = 1.18 mg/L (95% CI, 1.02-1.37 mg/L) and. EC50=1.18 mg/L (95% CI, 1.02-1.37 mg/L)
Reference substances (if used)	
Remarks fields for results	Affected fish lost schooling behavior, swam near tank bottom, and were hypoactive. Fish were darkly colored, had increased respiration, and lost equilibrium prior to death. Mortalities at 96 hrs: 2.12 mg/L 1/20; 3.26 mg/L, 9/20; 5.01 mg/L 20/20. No mortalities at lower concentrations.
Conclusion remarks	The LC50 of 2-dodecanone in fathead minnows in a flow-through system is reported to be 1.18mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Geiger D.L., Poirer S.H., Brooke L. T. and Call D.J., eds (1986) Acute toxicities of organic chemicals to fathead minnows (Pimephales Promelas). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior. Unpublished Report.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, 5-, and 6-dodecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	
Analytical monitoring	
Exposure period (unit)	96 hour
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 1.200 mg/L

Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for Substance	Calculated data for 2,3-, 2,4-, or 2,6-dimethylcyclohexanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	
Analytical monitoring	
Exposure period (unit)	96 hour
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 102.014 mg/L
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related ketone, 3-5,5-trimethyl-2-cyclhexenone.
Method/guideline	96-hr LC50
Test Type	Static
GLP	No
Year	1981
Species/Strain/Supplier	Fish/Bluegill
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Groups of 10, 30 day old fish were maintained at five different concentrations in flow-through systems for 96 hours in Lake Superior water. Deaths were recorded at 1, 3, 6, 12, 24, 48, 72, and 96 hours. Concentrations of test substance were measured daily by CG analysis. Water analyses: 24-26 C, hardness = 45.5 mg/L CaCO3, alkalinity = 42.2 mg/L, pH = 7.9 to 6.5, temperature 21-23C. Carrier solvent used 1,6-hexanediol, acetone, or dimethylformamide. LC50's were calculated by the log probit method (Litchfield and Wilcoxon, 1949).
Observations on precipitation	Test chemical formed slick on water surface.
Nominal concentrations as mg/L	Not given
Measured concentrations as mg/L	
Unit	
Endpoint value	LC50 = 220 mg/L (95% CI, 180-250 mg/L)
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	The acute 96-hr LC50 of isophorone in bluegills is estimated to be 220 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Buccafusco R.J., Ells S.J., and LeBlanc G. A. (1981) Acute toxicity of priority pollutants to Bluegill. Bulletin of Environmental

	Contaminant Toxicology, 26, 446-452.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	
Analytical monitoring	
Exposure period (unit)	96 hour
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 93.554 mg/L
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for dehydro analog, 6-methyl-5-hepten-2-one.

Method/guideline	96-hr LC50
Test Type	Flow-through
GLP	No
Year	1983
Species/Strain/Supplier	Minnows/Fathead/Environmental Research Laboratories/Duluth
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Groups of twenty to twenty-five 30 day old fish were maintained at five different concentrations in flow-through systems for 96 hours in Lake Superior water. Deaths were recorded at 1, 3, 6, 12, 24, 48, 72, and 96 hours. Concentrations of test substance were measured daily by CG analysis. Water analyses: 24-26 C, hardness = 45.5 mg/L CaCO3, alkalinity = 42.2 mg/L CaCO3, dissolved oxygen maintained at greater than 60% of saturation, pH = 7.5, 20-25 fish per dose, age = 30 day, weight = approximately 0.12 g.
Observations on precipitation	
Nominal concentrations as mg/L	Not given
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 85.7 mg/L
Reference substances (if used)	
Remarks fields for results	Substance was one of a series of 12 aliphatic ketones tested for acute toxicity in fathead minnows.
Conclusion remarks	The acute 96-hour LC50 of 6-methyl-5-hepten-2-one is 85.7 mg/L at 25+/-1C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Veith, G., Call, D., Brooke, L. (1983) Structure -Toxicity Relationships for Fathead Minnow (Pimephales promelas) Narcotic industrial chemicals. Canadian Journal of Fish. Aqua. Sci., 40, 743-748.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for isomer, 2-octanone.

Method/guideline	96-hr LC50
Test Type	Flow-through
GLP	Yes
Year	1985
Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Juvenile fathead minnows, 28-34 days of age, were treated with five concentrations of 2-octanone in a flow through system at 25 C. Fish were maintained on 16 hours of light and 8 hours of darkness during the test. Fish were not fed 24 hours prior to and during the test. Tank concentrations of the test agent were monitored daily by GLC. Water quality was monitored for dissolved oxygen (greater than 80% saturation), alkalinity (44.6 mg/L CaCO3), pH (7.6), and temperature (25+/-0.5C). Experiments at each concentration were performed in duplicate. LC50 and EC50 values were calculated using corrected average tank concentrations and the Trimmed Spearman-Karber method.
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	Acute 96-hr LC50 = 63 mg/L (95% CI, 60.9-65.2 mg/L)
Reference substances (if used)	
Remarks fields for results	Multiple acute test were run for 2-octanone.
Conclusion remarks	The acute 96-hr LC50 of 2-octanone in fathead minnows is 63 mg/L.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Broderius S. and Kahl M. (1985) Acute toxicity of organic chemical mixtures to the fathead minnow. Aquatic Toxicology, 6, 307-322.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone

Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	
Analytical monitoring	
Exposure period (unit)	96 hour
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 68.698 mg/L
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for isomer, 2-octanone.
Method/guideline	96-hr LC50
Test Type	
GLP	No
Year	1983

Species/Strain/Supplier	Minnows/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Groups of twenty to twenty-five 30 day old fish were maintained at five different concentrations in flow-through systems for 96 hours in Lake Superior water. Deaths were recorded at 1, 3, 6, 12, 24, 48, 72, and 96 hours. Concentrations of test substance were measured daily by CG analysis. Water analyses: 24-26 C, hardness = 45.5 mg/L CaCO3, alkalinity = 42.2 mg/L CaCO3, dissolved oxygen maintained at greater than 60% of saturation, pH = 7.5, 20-25 fish per dose, age= 30 day, weight = approximately 0.12 g.
Observations on precipitation	
Nominal concentrations as mg/L	Not given
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 36 mg/L
Reference substances (if used)	
Remarks fields for results	Substance was one of a series of 12 aliphatic ketones tested for acute toxicity in fathead minnows
Conclusion remarks	The acute 96-hour LC50 of 2-octanone is 36 mg/L at 25+/-1C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Veith, G., Call, D., Brooke, L. (1983) Structure -Toxicity Relationships for Fathead Minnow (Pimephales promelas) Narcotic industrial chemicals. Canadian Journal of Fish. Aqua. Sci., 40, 743-748.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for structurally related substance 2-hexanone,5-methyl-.
Method/guideline	
Test Type	Static
GLP	No
Year	1978

Species/Strain/Supplier	Minnow/Fathead
Analytical monitoring	GC Analysis
Exposure period (unit)	96 hour
Remarks for Test Conditions	Water was filter-treated lake water with residual chlorine chemically removed. 10 fish/concentration levels were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72 and 96 hours. Observations for stress and mortality were conducted at 0, 6, 24, 48, 72 and 96 hours.
Observations on precipitation	
Nominal concentrations as mg/L	100 ul/L
Measured concentrations as mg/L	
Unit	
Endpoint value	LC50 greater than 100 ul/L; NOEC > 100 ul/L
Reference substances (if used)	
Remarks fields for results	Exposure temperature was 19 deg C, pH ranged from 7.4 to 7.9, and dissolved oxygen ranged from 4.8 to 8.7 mg/L.
Conclusion remarks	The acute 96-hr LC50 =100 ul/L LC50 value indicates that the test substance would not be classified according to the European Union's labelling directive and would correspond to a "low concern level" according to the US EPA's assessment criteria.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Eastman Kodak Co. (1978) An acute aquatic effects test with the Fathead Minnow (Pimephales promelas);Environmental Sciences Section, Health and Environment Laboratories, HAEL No. 78-0260.
CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	

Year	
Species/Strain/Supplier	Fish
Analytical monitoring	
Exposure period (unit)	96 hours
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 3.788 mg/L
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	Fish
Analytical monitoring	
Exposure period (unit)	96 hours
Remarks for Test Conditions	

Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
Endpoint value	96-hr LC50 = 14.95 mg/L
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Calculated data for 2-, 6-, and 8-Pentadecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Species/Strain/Supplier	Fish
Analytical monitoring	
Exposure period (unit)	96 hours
Remarks for Test Conditions	
Observations on precipitation	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	

Endpoint value	96-hr LC50 = 0.061 mg/L
Reference substances (if used)	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

3.2 Acute Toxicity to Aquatic Invertebrates

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, or 5-nonanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	96 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	96-hr LC50 = 26.52 at 25 °C
Biological observations	

Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	925-78-0
Substance Name	3-Nonanone
Remarks for Substance	Data are for homologue, 3-octanone.
Method/guideline	Experimental
Test Type	24-hour LC50 static test
GLP	No
Year	1977
Analytical procedures	
Species/Strain	Daphnia magna
Test details	24 hours
Remarks for Test Conditions	Daphnia magna (30/group, 24 hours old) were maintained in chlorine free tap water saturated with oxygen, pH of 7.7-7.7 and temperature of 20-22 °C. The LC50, LC0 and LC100 were determined.
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
EC50, EL50, LC0, at 24,48 hours	24 hour LC50 = 517, LC0 = 175 mg/mL
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	

Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	The study was reported in German with an English summary, but the results are considered reliable.
References	Bringmann G. and Kuehn, R. (1977) Befunde der Schadwirkung wassergefaehrdender Stoffe gegen Daphnia magna. [Results of the damaging effects of water pollutants on Daphnia magna.] A Wasser Abwasser Forsch., 10(5), :161-166.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, or 5-decanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	96 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	96-hr LC50 = 10.04 at 25 °C
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.

Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, 5- or 6-undecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	96 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	96-hr LC50 = 3.92 at 25 °C
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, 5- or 6-dodecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	96 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	96-hr LC50 = 1.52 at 25 °C
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	
Method/guideline	ECOSAR

Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	96 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	96-hr LC50 = 93.55 at 25 °C
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for Substance	Calculated data for 2,3-, 2,4-, or 2,6-dimethylcyclohexanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	

Analytical procedures	
Species/Strain	Daphnia magna
Test details	96 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	96-hr LC50 = 109.0 at 25 °C
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for Substance	Data are for homologue, 2-methylcyclohexanone.
Method/guideline	Experimental
Test Type	24-hour LC50 static test
GLP	No
Year	1977
Analytical procedures	
Species/Strain	Daphnia magna
Test details	24 hours

Remarks for Test Conditions	Daphnia magna (30/group, 24 hours old) were maintained in chlorine free tap water saturated with oxygen, pH of 7.7-7.7 and temperature of 20-22 C. The LC50, LC0 and LC100 were determined.
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
EC50, EL50, LC0, at 24,48 hours	24 hour LC50 = 435, LC0 = 125, LC100 = 1000 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	The study was reported in German with an English summary, but the results are considered reliable.
References	Bringmann G. and Kuehn, R. (1977) Befunde der Schadwirkung wassergefaehrdender Stoffe gegen Daphnia magna. [Results of the damaging effects of water pollutants on Daphnia magna.] A Wasser Abwasser Forsch., 10(5), 161-166.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	96 hours
Remarks for Test Conditions	

Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	96-hr LC50 = 74.38 at 25 °C
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for structurally related substance 5-methyl-2-hexanone.
Method/guideline	
Test Type	Acute immobilization, Static
GLP	No
Year	1978
Analytical procedures	Yes, exposure solutions, temp., pH, dissolved oxygen
Species/Strain	Daphnid/daphnia magna
Test details	96 hour
Remarks for Test Conditions	Water was filter-treated lake water with residual chlorine chemically removed. 10 Daphnids per dose level were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96-hours. Observations for stress and mobility were conducted at 0, 6, 24, 48, 72 and 96 hours.
Nominal concentrations as mg/L	100 ul/L

Measured concentrations as mg/L	
Unit	
EC50, EL50, LC0, at 24,48 hours	EC50 96-hour greater than 100 ul/L; NOEC greater than 100 ul/L.
Biological observations	The Daphnia exhibited behaviour comparable to controls at all test concentrations.
Control response satisfactory	
Appropriate statistical evaluations	NA; no effects were noted at this concentration.
Remarks fields for results	Exposure temperature remained at 19 °C throughout the test, pH was 7.4-7.9, and dissolved oxygen was 4.8-8.7 mg/L.
Conclusion remarks	The LC50 value indicated that the test substance would not be classified according to the European Union's labelling directive and would correspond to a "low concern level" according to the US EPA's assessment criteria.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Eastman Kodak Co. (2000) An acute aquatic effects test with the Daphnid (*daphnia magna*); Environmental Sciences Section, Health and Environment Laboratories, HAEL No. 78-0260.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for homologue, 5-methyl-2-hexanone.
Method/guideline	Experimental
Test Type	24-hour LC50 static test
GLP	No
Year	1977
Analytical procedures	
Species/Strain	Daphnia magna
Test details	24 hours
Remarks for Test Conditions	Daphnia magna (30/group, 24 hours old) were maintained in chlorine free tap water saturated with oxygen, pH of 7.7-7.7 and temperature of 20-22 °C. The LC50, LC0 and LC100 were determined.

Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	
EC50, EL50, LC0, at 24,48 hours	24 hour LC50 = 170, LC0 = 910, LC100 = 2000 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	The study was reported in German with an English summary, but the results are considered reliable.
References	Bringmann G. and Kuehn, R. (1977) Befunde der Schadwirkung wassergefaehrdender Stoffe gegen Daphnia magna. [Results of the damaging effects of water pollutants on Daphnia magna.] A Wasser Abwasser Forsch., 10(5), 161-166.
CAS	5440-89-1
Substance Name	5-Ethyl-2-nonanone
Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	48 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	

Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hour LC50 = 4.54 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Calculated data for 2-, 6-, or 8-Pentadecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	48 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hour LC50 = 0.084 mg/L
Biological observations	
Control response	

satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	67662-98-0
Substance Name	3-Methyl-5-propylcyclohexanone
Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	
Analytical procedures	
Species/Strain	Daphnia magna
Test details	48 hours
Remarks for Test Conditions	
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hour LC50 = 17.09 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Assay greater than 95%, Data are for homolog, 2-octanone.
Method/guideline	Schultz, 1990
Test Type	48 hr EC50 test
GLP	No
Year	1990
Analytical procedures	
Species/Strain	*Tetrahymena pyriformis*
Test details	48 hours
Remarks for Test Conditions	48 hour population densities of axanic cultures of tetrahymena pyriformis were measured spectraphotometrically at 540 nm. Each chemical was tested in duplicate for at least 3 replicates. Each replicate was a five step graded concentration series. The 5
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hr EC50 = 224 mg/L
Biological observations	Abiotic loss of ketones was between 20-60% over the 48 hr period.
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis of SAS Institute, 1985.
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 2-octanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 224 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. Wyatt N.L., Lin D.T. (1990) Structure-toxicity of nonpolar narcotics: A comparison of data from the Tetrahymen, Photobacterium and Pimephales systems.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	
Method/guideline	TETRATOX Assay
Test Type	40 hr IGC50 test
GLP	No
Year	1997
Analytical procedures	GC Analysis
Species/Strain	*Tetrahymena pyriformis*
Test details	40 hour
Remarks for Test Conditions	A 40 hour static assay was conducted to measure the 50% growth inhibitory concentration of the test substance on *Tetrahymena pyriformis*. The test was allowed to run through 8-9 cell cycles. Semi-defined proteose-peptone-based medium were inoculated to a dens
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	40-hr IGC50 = 33.26 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis (Finney, 1971)
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 2-nonanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 33.26 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. (1997) TETRATOX: *Tetrahymena pyriformis* population growth impairment endpoint-asurrogate for fish lethality. Toxicology Methods, 7, 289-309.
CAS	4485-09-0
Substance Name	4-Nonanone
Remarks for Substance	Assay greater than 95%, Data are for homolog, 4-heptanone.
Method/guideline	Schultz, 1990
Test Type	48 hr EC50 test
GLP	No
Year	1990
Analytical procedures	
Species/Strain	*Tetrahymena pyriformis*
Test details	48 hours
Remarks for Test Conditions	48 hour population densities of axanic cultures of tetrahymena pyriformis were measured spectraphotometrically at 540 nm. Each chemical was tested in duplicate for at least 3 replicates. Each replicate was a five step graded concentration series. The 5
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hr EC50 = 679 mg/L
Biological observations	Abiotic loss of ketones was between 20-60% over the 48 hr period.
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis of SAS Institute, 1985.
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 4-heptanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 679 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. Wyatt N.L., Lin D.T. (1990) Structure-toxicity of nonpolar narcotics: A comparison of data from the Tetrahymen, Photobacterium and Pimephales systems.
CAS	502-56-7
Substance Name	5-Nonanone
Remarks for Substance	Assay greater than 95%
Method/guideline	Schultz, 1990
Test Type	48 hr EC50 test
GLP	No
Year	1990
Analytical procedures	
Species/Strain	*Tetrahymena pyriformis*
Test details	48 hours
Remarks for Test Conditions	48 hour population densities of axanic cultures of tetrahymena pyriformis were measured spectraphotometrically at 540 nm. Each chemical was tested in duplicate for at least 3 replicates. Each replicate was a five step graded concentration series. The 5
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hr EC50 = 145 mg/L
Biological observations	Abiotic loss of ketones was between 20-60% over the 48 hr period.
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis of SAS Institute, 1985.
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 5-nonanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 145 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. Wyatt N.L., Lin D.T. (1990) Structure-toxicity of nonpolar narcotics: A comparison of data from the Tetrahymen, Photobacterium and Pimephales systems.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Assay greater than 95%
Method/guideline	Schultz, 1990
Test Type	48 hr EC50 test
GLP	No
Year	1990
Analytical procedures	
Species/Strain	*Tetrahymena pyriformis*
Test details	48 hours
Remarks for Test Conditions	48 hour population densities of axanic cultures of tetrahymena pyriformis were measured spectraphotometrically at 540 nm. Each chemical was tested in duplicate for at least 3 replicates. Each replicate was a five step graded concentration series. The 5
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	48-hr EC50 = 49.3 mg/L
Biological observations	Abiotic loss of ketones was between 20-60% over the 48 hr period.
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis of SAS Institute, 1985.
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 2-Decanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 49.3 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. Wyatt N.L., Lin D.T. (1990) Structure-toxicity of nonpolar narcotics: A comparison of data from the Tetrahymen, Photobacterium and Pimephales systems.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	
Method/guideline	TETRATOX Assay
Test Type	40 hr IGC50 test
GLP	No
Year	1997
Analytical procedures	GC Analysis
Species/Strain	*Tetrahymena pyriformis*
Test details	40 hour
Remarks for Test Conditions	A 40 hour static assay was conducted to measure the 50% growth inhibitory concentration of the test substance on *Tetrahymena pyriformis*. The test was allowed to run through 8-9 cell cycles. Semi-defined proteose-peptone-based medium were inoculated to a dens
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	40-hr IGC50 = 44.21 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis (Finney, 1971)
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 2-decanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 44.21 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. (1997) TETRATOX: *Tetrahymena pyriformis* population growth impairment endpoint-asurrogate for fish lethality. Toxicology Methods, 7, 289-309.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	
Method/guideline	TETRATOX Assay
Test Type	40 hr IGC50 test
GLP	No
Year	1997
Analytical procedures	GC Analysis
Species/Strain	*Tetrahymena pyriformis*
Test details	40 hour
Remarks for Test Conditions	A 40 hour static assay was conducted to measure the 50% growth inhibitory concentration of the test substance on Tetrahymena pyriformis. The test was allowed to run through 8-9 cell cycles. Semi-defined proteose-peptone-based medium were inoculated to a dens
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	40-hr IGC50 = 5.76 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis (Finney, 1971)
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 2-undecanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 5.76 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. (1997) TETRATOX: *Tetrahymena pyriformis* population growth impairment endpoint-asurrogate for fish lethality. Toxicology Methods, 7, 289-309.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	
Method/guideline	TETRATOX Assay
Test Type	40 hr IGC50 test
GLP	No
Year	1997
Analytical procedures	GC Analysis
Species/Strain	*Tetrahymena pyriformis*
Test details	40 hour
Remarks for Test Conditions	A 40 hour static assay was conducted to measure the 50% growth inhibitory concentration of the test substance on *Tetrahymena pyriformis*. The test was allowed to run through 8-9 cell cycles. Semi-defined proteose-peptone-based medium were inoculated to a dens
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
EC50, EL50, LC0, at 24,48 hours	40-hr IGC50 = 5.76 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	Yes, Probit Anaylsis (Finney, 1971)
Remarks fields for results	
Conclusion remarks	Under conditions of the experiment the concentration of 2-undecanone required for 50% growth inhibition of *Tetrahymena pyriformis* is 5.76 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Schultz, T.W. (1997) TETRATOX: *Tetrahymena pyriformis* population growth impairment endpoint-asurrogate for fish lethality. Toxicology Methods, 7, 289-309.

3.3 Acute Toxicity to Aquatic Plants

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data are for structurally related substance 2-heptanone, purity 99.8%.
Method/guideline	OECD: TG-201
Test Type	Growth inhibition of algae
GLP	Yes
Year	1998
Species/Strain/Supplier	Selenastrum capricornutum
Endpoint basis	Cell concentrations and growth rate
Exposure period (duration)	72 hours
Analytical monitoring	Temp., light intensity, rpm, test substance
Remarks for Test Conditions	
Nominal concentrations as mg/L	12.5, 25, 50, 100 and 200
Measured concentrations as mg/L	6.2, 11.9, 22.1, 42.7, 86.3 mg/L
Unit	
Endpoint value	0-72 hr - EbC50 was 75.5 mg/L; ErC50 was 98.2 mg/L
NOEC, LOEC or NOEL, LOEL	72 hour NOEC was estimated to be 42.7 mg/L
Biological observations	No deformed cells were noted.
Control response satisfactory	Yes
Appropriate statistical evaluations	

Remarks fields for results	A mean illumination of 741 +/- 1.7 foot-candles was maintained. The mean temperature was 24 °C and pH ranged from 7.3-7.7. Cultures were oscillated at 100 rpm. The significant loss (up to 82% over the course of the study) in the material was attributed to volatilization. No protocol deviations were noted.
Conclusion remarks	The 72-hour EbC50 and ErC50 values indicate that the test substance would be classified as "harmful to aquatic organisms" according to the European Union's labelling directive and would be classified in a "moderate concern level" according to US EPA's.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Eastman Kodak Co. (1998) A growth inhibition test with alga, Selenastrum capricornutum. Enviromental Sciences Section, Health and Environment Laboratories, Eastman Kodak Co., Rochester, NY.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, or 5-nonanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	2000
Species/Strain/Supplier	Green algae
Endpoint basis	
Exposure period (duration)	96 hours
Analytical monitoring	
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
Endpoint value	
NOEC, LOEC or NOEL, LOEL	96-hr EC50 =16.62 mg/L
Biological observations	

Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data are for structurally related substance 2-heptanone.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	2000
Species/Strain/Supplier	Green algae
Endpoint basis	
Exposure period (duration)	96 hours
Analytical monitoring	
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
Endpoint value	
NOEC, LOEC or NOEL, LOEL	96-hr EC50 = 98.3 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	

Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, or 5-decanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	2000
Species/Strain/Supplier	Green algae
Endpoint basis	
Exposure period (duration)	96 hours
Analytical monitoring	
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
Endpoint value	
NOEC, LOEC or NOEL, LOEL	96-hr EC50 =6.728 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, 5-, or 6-undecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	2000
Species/Strain/Supplier	Green algae
Endpoint basis	
Exposure period (duration)	96 hours
Analytical monitoring	
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
Endpoint value	
NOEC, LOEC or NOEL, LOEL	96-hr EC50 = 2.701 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Calculated data for 2-, 3-, 4-, 5-, or 6-dodecanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	2000
Species/Strain/Supplier	Green algae
Endpoint basis	
Exposure period (duration)	96 hours
Analytical monitoring	
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
Endpoint value	
NOEC, LOEC or NOEL, LOEL	96-hr EC50 =1.077 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Calculated data for 3,3-, 2,3-, 2,4-, or 2,6-dimethylcyclohexanone are equivalent.
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	2000
Species/Strain/Supplier	Green algae
Endpoint basis	
Exposure period (duration)	96 hours
Analytical monitoring	
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
Endpoint value	
NOEC, LOEC or NOEL, LOEL	96-hr EC50 =62.67 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone

Remarks for Substance	Data are for structurally related substance 2-hexanone, 5-methyl-, purity 99.8%.
Method/guideline	OECD: TG-201
Test Type	Growth inhibition of algae
GLP	Yes
Year	2001
Species/Strain/Supplier	Selenastrum capricornutum
Endpoint basis	Cell concentrations and growth rate
Exposure period (duration)	72 hours
Analytical monitoring	Temp., light intensity, rpm, test substance
Remarks for Test Conditions	
Nominal concentrations as mg/L	12.5, 25, 50, 100 and 200
Measured concentrations as mg/L	6.2, 11.9, 22.1, 42.7, 86.3 mg/L
Unit	
Endpoint value	0-72 hr - EbC50 was 75.5 mg/L; ErC50 was 98.2 mg/L
NOEC, LOEC or NOEL, LOEL	72 hour NOEC was estimated to be 42.7 mg/L
Biological observations	No deformed cells were noted
Control response satisfactory	Yes
Appropriate statistical evaluations	
Remarks fields for results	A mean illumination of 741 +/- 1.7 foot-candles was maintained. The mean temperature was 24 deg C and pH ranged from 7.3-7.7. Cultures were oscillated at 100 rpm. The significant loss (up to 82% over the course of the study) in the material was attributed t volatilization. No protocol deviations were noted.
Conclusion remarks	The 72-hour EbC50 and ErC50 values indicate that the test substance would be classified as "harmful to aquatic organisms" according to the European Union's labelling directive and would be classified in a "moderate concern level" according to US EPA's.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Eastman Kodak Co. (2001a) A growth inhibition test with alga, Selenastrum capricornutum. Enviromental Sciences Section, Health and Environment Laboratories, Eastman Kodak Co., Rochester, NY.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	
Method/guideline	ECOSAR
Test Type	Calculated
GLP	
Year	2000
Species/Strain/Supplier	Green algae
Endpoint basis	
Exposure period (duration)	96 hours
Analytical monitoring	
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Nominal concentrations as mg/L	
Measured concentrations as mg/L	
Unit	mg/L
Endpoint value	
NOEC, LOEC or NOEL, LOEL	96-hr EC50 =46.902 mg/L
Biological observations	
Control response satisfactory	
Appropriate statistical evaluations	
Remarks fields for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

4 HUMAN HEALTH TOXICITY

4.1 Acute Toxicity

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	
Method/guideline	
Test Type	Acute Oral Toxicity LD 50
GLP	No
Year	1986
Species/Strain	Mice/ddY
Sex	Male
# of animals per sex per dose	4 per dose
Vehicle	Olive Oil
Route of administration	Oral-Gavage
Remarks for test conditions	The acute oral LD 50 was determined using 4 male dd Y mice (24-27 g) per dose. Mice were pre-treated with an intraperitoneal injection of olive oil. Tests were conducted with four concentrations.
Value LD50 or LC50 with confidence limits	7879 gm/kg (95 % CI, 5538-9552 mg/kg) 5465-9535 mg/kg/kg
Number of deaths at each dose level	Not given
Remarks for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Tanii, H., Tsuji, H., Hashimoto, K. (1986) Structure -Toxicity Relationship of Monoketones. Toxicology Letters, 30(1), 13-17.

CAS	821-55-6
Substance Name	2-Nonanone

Remarks for Substance	Assay greater than 95%
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute Oral Toxicity LD 50
GLP	Yes
Year	1980
Species/Strain	Rat
Sex	Male
# of animals per sex per dose	10
Vehicle	None
Route of administration	Oral-Gavage
Remarks for test conditions	The rats were observed once daily for 14 days. Mortality, toxicity, and pharmacological effects were recorded.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg
Number of deaths at each dose level	1/10
Remarks for results	9/10 rats survived and oral dose of 5.0 g/kg. Toxic signs included lethargy, ataxia prostration, flaccid muscle tone, ptosis and tachypnea. Internal Organs appeared normal on superficial examination, except for lung, heart, and gastrointestinal abnormalities noted in one animal death.
Conclusion remarks	Study conducted in Accordance with FDA's Good Laboratory Practices, 1979
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. (1980) Acute Toxicity Studies. Project No. MB80-4817A. Unpublished report to RIFM.

CAS	925-78-0
Substance Name	3-Nonanone
Remarks for Substance	
Method/guideline	
Test Type	Acute Oral Toxicity
GLP	No
Year	1967

Species/Strain	Mouse/CF-1
Sex	Male and Female
# of animals per sex per dose	10/group
Vehicle	None
Route of administration	Oral-Gavage
Remarks for test conditions	Male and female CF-1 mice weighing 17-25 grams were given a single oral dose of the test substance and observed for 72 hours.
Value LD50 or LC50 with confidence limits	5270 mg/kg (CI, =/- 542.5 mg/L kg
Number of deaths at each dose level	Not given
Remarks for results	
Conclusion remarks	The acute oral LD50 of 3-nonanone in CF-1 mice is 5270 mg/kg
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hoffman-LaRoche (1967) Acute toxicity, eye, and skin irritation tests of fragrance materials. Unpublished Report to the Research Institute for Fragrance Materials.
CAS	693-54-9
Substance Name	2-Decanone
Remarks for Substance	
Method/guideline	
Test Type	Acute Oral Toxicity LD 50
GLP	No
Year	1986
Species/Strain	Mice/ddY
Sex	Male
# of animals per sex per dose	4 per dose
Vehicle	Olive Oil
Route of administration	Oral-Gavage
Remarks for test conditions	The acute oral LD 50 was determined using 4 male dd Y mice (24-27 g) per dose. Mice were pre-treated with an

	intraperitoneal injection of olive oil. Tests were conducted with four concentrations.
Value LD50 or LC50 with confidence limits	7940 gm/kg (95 % CI, 3847- 16317 mg/kg) 5465-9535 mg/kg/kg 5465-9535 mg/kg/kg
Number of deaths at each dose level	Not given
Remarks for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Tanii, H., Tsuji, H., Hashimoto, K. (1986) Structure -Toxicity Relationship of Monoketones. Toxicology Letters, 30(1), 13-17.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute Dermal LD50
GLP	No
Year	1974
Species/Strain	Rabbit
Sex	Not reported
# of animals per sex per dose	4
Vehicle	None
Route of administration	Dermal
Remarks for test conditions	4 Rabbits were used. Animals were observed for mortality and systemic effects over a 14 day period.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg
Number of deaths at each dose level	No deaths
Remarks for results	
Conclusion remarks	The oral LD50 of 2-undecanone in rats exceeds 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Levenstein I. (1974) Acute toxicity study in rats and rabbits. Unpublished report to RIFM.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute Oral LD 50
GLP	No
Year	1974
Species/Strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of administration	Oral-Gavage
Remarks for test conditions	10 Rats were used. Animals were observed for mortality and systemic effects over a 14 day period.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg
Number of deaths at each dose level	No Deaths. Gross pathology performed on animals surviving to 14 days revealed no changes that could be associated with administration of the test substance.
Remarks for results	
Conclusion remarks	The oral LD50 of 2-nonanone in rats exceeds 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Levenstein, I. (1974) Acute toxicity study in rats and rabbits. Unpublished report to RIFM.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	

Method/guideline	
Test Type	Acute Oral Toxicity LD 50
GLP	No
Year	1986
Species/Strain	Mice/ddY
Sex	Male
# of animals per sex per dose	4 per dose
Vehicle	Olive Oil
Route of administration	Oral-Gavage
Remarks for test conditions	The acute oral LD 50 was determined using 4 male dd Y mice (24-27 g) per dose. Mice were pre-treated with an intraperitoneal injection of olive oil. Tests were conducted with four concentrations.
Value LD50 or LC50 with confidence limits	19448 gm/kg (95 % CI, 11900-31790 mg/kg) 5465-9535 mg/kg/kg 5465-9535 mg/kg/kg
Number of deaths at each dose level	Not given
Remarks for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Tanii, H., Tsuji, H., Hashimoto, K. (1986) Structure -Toxicity Relationship of Monoketones. Toxicology Letters, 30(1), 13-17.
CAS	6175-49-1
Substance Name	2-Dodecanone
Remarks for Substance	Data are for homologue, 2-tridecanone.
Method/guideline	
Test Type	Acute Toxicity
GLP	Yes
Year	2000
Species/Strain	Rat/Sprague-Dawley
Sex	Male and Female

# of animals per sex per dose	5
Vehicle	Olive oil
Route of administration	Oral-Gavage
Remarks for test conditions	Male and female rats, 161-191 gm body weight, were administered the test compound neat and observed regularly for 24 hours and then daily for the next 14 days. At the conclusion of the study all animals were sacrificed and subjected to gross pathological
Value LD50 or LC50 with confidence limits	Greater than 2000 mg/kg
Number of deaths at each dose level	
Remarks for results	No deaths or effects in either sex
Conclusion remarks	The oral LD50 of 2-tridecanone in rats exceeds 2000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Dragoco Gerberding and Co. GmbH (2000) Acute toxicity study of 2-tridecanone by oral administration to Sprague-Dawley rats. Unpublished report.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related substance, 3,5,5-trimethylcyclohexenone.
Method/guideline	Wilcoxon & Litchfield method
Test Type	Acute Oral LD50
GLP	No
Year	1982
Species/Strain	Rat/Sprague-Dawley albino
Sex	Male
# of animals per sex per dose	5
Vehicle	None
Route of administration	Oral
Remarks for test conditions	Test substance(s) were administered to 6 groups of five male albino Sprague-Dawley animals. Animals were fasted 3 to 4 hours prior to dosing. Animals were observed at 1, 4, 24 hours

	immediately after compound administration and once daily thereafter for a total of 14 days. Necropsy was conducted.
Value LD50 or LC50 with confidence limits	3450 mg/kg
Number of deaths at each dose level	
Remarks for results	Animals exhibited depression, ptosis, lacrimation, labored respiration & evidence of excessive urination. Congestion of lungs, kidneys, adrenals, & pancreas and gastrointestinal inflammation were observed.
Conclusion remarks	The acute oral LD50 of 3,5,5-trimethylcyclohexenone in rats is 3450 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Exxon Chemical Americas (1982) Unpublished report to Environmental Protection Agency.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related substance, 3,5,5-trimethylcyclohexenone
Method/guideline	Wilcoxon & Litchfield method
Test Type	Acute Inhalation toxicity
GLP	No
Year	1982
Species/Strain	Rat/Wistar
Sex	Male
# of animals per sex per dose	10
Vehicle	None
Route of administration	Inhalation
Remarks for test conditions	Groups of 10 male Wistar animals were exposed to various doses of test material. Each exposure was for 4 hours. Animals were observed approximately every 30 minutes for toxic signs and death. Following exposure animals were observed daily for 14 days for toxic signs and death. Gross necropsies were performed.
Value LD50 or LC50 with confidence limits	7/mg/L (1281 ppm)

Number of deaths at each dose level	
Remarks for results	Animals exhibited dyspnea, piloerection, depression, & decreased activity.
Conclusion remarks	The acute inhalation LD50 of 3,5,5-trimethylcyclohexenone in Wistar rats is 7 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Exxon Chemical Americas (1982) Unpublished report to Environmental Protection Agency.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for dehydro derivative, 6-methyl-5-hepten-2-one.
Method/guideline	
Test Type	Acute Oral Toxicity LD 50
GLP	No
Year	1972
Species/Strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of administration	Oral-Gavage
Remarks for test conditions	
Value LD50 or LC50 with confidence limits	4100 mg/kg (95% CI, 3330-5040 mg/kg)
Number of deaths at each dose level	
Remarks for results	Symptomatology: Immediate stimulation followed by ataxia
Conclusion remarks	The acute oral LD50 of 6-methyl-5-hepten-2-one in rats is 4100 mg/kg
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Keating J. (1972) Acute oral toxicity in rats, dermal toxicity in rabbits. Unpublished report to RIFM dated June 7, 1972.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for dehydro derivative, 6-methyl-5-hepten-2-one.
Method/guideline	
Test Type	Acute Dermal Toxicity LD 50
GLP	No
Year	1972
Species/Strain	Rabbit
Sex	Not reported
# of animals per sex per dose	6
Vehicle	None
Route of administration	Dermal
Remarks for test conditions	6 Rabbits per dose were used. Animals were observed for mortality and clinical signs over a period of 14 days.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg
Number of deaths at each dose level	
Remarks for results	1/6 Deaths. Death occurred on day 9. Acute dermal LD 50 greater than 5000 mg/kg.
Conclusion remarks	The dermal LD50 of 6-methyl-5-hepten-2-ne in rabbis is greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Keating J. (1972) Acute oral toxicity in rats, dermal toxicity in rabbits. Unpublished report to RIFM dated June 7, 1972.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data for dehydro derivative, 6-methyl-5-hepten-2-one
Method/guideline	
Test Type	Acute Inhalation toxicity
GLP	No

Year	1974
Species/Strain	Rat
Sex	Not reported
# of animals per sex per dose	12
Vehicle	None
Route of administration	Inhalation
Remarks for test conditions	Air was passed through a 5-cm thick layer of the chemical. Atmosphere was saturated with steam at 20 C. 12 animals were exposed for 8 hours and observed.
Value LD50 or LC50 with confidence limits	No effects to an atmosphere saturated with the test material at 20 C.
Number of deaths at each dose level	0/12 deaths were observed
Remarks for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	BASF (1974) Acute toxicity studies on 6-methyl-5-hepten-2-one. Unpublished report.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for dehydro derivative, 6-methyl-5-hepten-2-one.
Method/guideline	
Test Type	Acute Oral LD50
GLP	No
Year	1974
Species/Strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of administration	Oral-Gavage

Remarks for test conditions	The approximate peroral LD 50 in rats was determined
Value LD50 or LC50 with confidence limits	Greater than 4200 ul/kg
Number of deaths at each dose level	0/12
Remarks for results	
Conclusion remarks	The oral LD50 of 6-methyl-5-hepten-2-one in rats is greater than 4200 ul/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	BASF (1974) Acute toxicity studies on 6-methyl-5-hepten-2-one. Unpublished report.

4.2 Genetic Toxicity

4.2.1 *In vitro* Genotoxicity

CAS	4485-09-0
Substance Name	4-Nonanone
Remarks for Substance	Data are for isomer, 2,6-dimethyl-4-heptanone.
Method/guideline	Ames Test
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1986
Species/Strain	Salmonella typhimurium TA 100, TA98, TA97, TA1535, and TA1537
Metabolic Activation	Male Sprague Dawley rat liver microsome fraction S9 from Aroclor induced rats.
Doses/concentration levels	1-333 ug per plate
Statistical Methods	Not given
Remarks for test conditions	After 48-hour incubation at 37 C, each assay plate was counted. Routine positive control plates were prepared: sodium azide for TA1535 and TA100, 4-nitro-o-phenylenediamine for

	TA98, and 9-aminoacridine for TA97 and TA1537, 2-aminoanthracen.
Result	No mutagenic effects
Cytotoxic concentration	
Genotoxic effects	None
Appropriate statistical evaluations	None given
Remarks for results	
Conclusion remarks	No mutagenic activity of 2,6-dimethyl-4-heptanone was observed using Salmonella typhimurium strains TA98, TA100, TA1535 & TA1538 in the presence or absence of S9 fraction.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B and Zeiger, E. (1986) Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. Environmental Mutagenesis 8(Supplement 7): 1-119.
CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Data are for homologous ketone, 6,10-dimethyl-2-undecatrienone.
Method/guideline	Ames Test
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	Salmonella typhimurium strains TA98, TA100, TA1535 & TA1537
Metabolic Activation	With and without S9 fraction rat liver treated with Aroclor 1254
Doses/concentration levels	3 micromol/plate , then at 0.03, 0.3, 3, and 30 umole/plate
Statistical Methods	Not given
Remarks for test conditions	The solvent used was ethanol. Only one replicate was performed for the substances which tested negative. Similar to OECD 471. No E. coli strain was included.
Result	No mutagenic effects at any concentration.

Cytotoxic concentration	Not given
Genotoxic effects	None
Appropriate statistical evaluations	None given
Remarks for results	
Conclusion remarks	No mutagenic activity of 6,10-dimethyl-2-undecatrienone was observed using Salmonella typhimurium strains TA98, TA100, TA1535 & TA1538 in the presence or absence of S9 fraction.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Florin, I., Rutberg, L., Curvall, M. and Enzell, C. R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18: 219-232.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data are for homologous ketone, tetramethylethylcyclohexanone.
Method/guideline	Ames Test
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1983
Species/Strain	Salmonella typhimurium TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/concentration levels	up to 3.6 mg/plate
Statistical Methods	Method of Kastenbaum and Bowman (1970)
Remarks for test conditions	Positive controls were run in each experiment with the reference mutagens sodium azide and benzo(a)pyrene
Result	No mutagenic effects
Cytotoxic concentration	Not given
Genotoxic effects	None
Appropriate statistical evaluations	None given
Remarks for results	

Conclusion remarks	No mutagenic effects
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Wild, D., King, M.-T., Gocke, E. and Eckhardt, K. (1983) Study of Artifical Flavouring Susbtances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. Fd. Chem. Toxic. 21(6): 707-719.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for homologous ketone, 2,2,6-trimethylcyclohexanone
Method/guideline	Ames Test
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	Salmonella typhimurium strains TA98 and TA100
Metabolic Activation	With and without S9 fraction rat liver treated with Aroclor 1254
Doses/concentration levels	3 micromol/plate , then at 0.03, 0.3, 3, and 30 umole/plate
Statistical Methods	Not given
Remarks for test conditions	The solvent used was ethanol. Only one replicate was performed for the substances which tested negative. Similar to OECD 471. No E. coli strain was included.
Result	No mutagenic effects at any concentration.
Cytotoxic concentration	
Genotoxic effects	None
Appropriate statistical evaluations	None given
Remarks for results	
Conclusion remarks	No mutagenic activity of 2,2,6-trimethylcyclohexanone was observed using Salmonella typhimurium strains TA98and TA100.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.

References	Florin, I., Rutberg, L., Curvall, M. and Enzell, C. R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18: 219-232.
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for isomer structurally related ketone, 3,5,5-dimethylcyclohexenone.
Method/guideline	Ames Test
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1986
Species/Strain	Salmonella typhimurium TA 100, TA98, TA1535, and TA1537
Metabolic Activation	Male Sprague Dawley rat liver microsome fraction S9 from Aroclor induced rats.
Doses/concentration levels	1-10,000 ug per plate
Statistical Methods	Not given
Remarks for test conditions	After 48-hour incubation at 37 C, each assay plate was counted. Routine positive control plates were prepared: sodium azide for TA1535 and TA100, 4-nitro-o-phenylenediamine for TA98, and 9-aminoacridine for TA97 and TA1537, 2-aminoanthracen
Result	No mutagenic effects
Cytotoxic concentration	
Genotoxic effects	None
Appropriate statistical evaluations	None given
Remarks for results	
Conclusion remarks	No mutagenic activity was observed upon incubation of 3,5,5-trimethylcyclohexenone with Salmonella typhimurium strains TA98, TA100, TA1535 & TA1538 in the presence or absence of S9 fraction.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B and Zeiger, E. (1986) Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. Environmental

Mutagenesis 8(Supplement 7): 1-119.

CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for homologous ketone, 6-methyl-5-hepten-2-one.
Method/guideline	Ames Test
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	Salmonella typhimurium strains TA98, TA100, TA1535 & TA1537
Metabolic Activation	With and without S9 fraction rat liver treated with Aroclor 1254
Doses/concentration levels	3 micromol/plate , then at 0.03, 0.3, 3, and 30 umole/plate
Statistical Methods	Not given
Remarks for test conditions	The solvent used was ethanol. Only one replicate was performed for the substances which tested negative. Similar to OECD 471. No E. coli strain was included.
Result	No mutagenic effects at any concentration.
Cytotoxic concentration	
Genotoxic effects	None
Appropriate statistical evaluations	None given
Remarks for results	
Conclusion remarks	No mutagenic activity of 6-methyl-5-hepten-2-one was observed using Salmonella typhimurium strains TA98, TA100, TA1535 & TA1538 in the presence or absence of S9 fraction.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Florin, I., Rutberg, L., Curvall, M. and Enzell, C. R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18: 219-232.

4.2.2 *In vivo* Genotoxicity

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data for structurally related ketone, 3,5,5-trimethylcyclohexenone
Method/guideline	
Test Type	Clastogenicity assay
GLP	Ambiguous
Year	1988
Species/Strain	Mouse/CD-1
Sex	Male and Female
Route of administration	Intraperitoneal
Doses/concentration levels	0.54 ml/kg
Exposure period	48 hours
Remarks for test conditions	Groups of male and female CD-1 mice were given a single oral dose of the test material in corn oil and sacrificed at 12, 24 and 48 hours. A positive control group was given 0.25 ml/kg of triethylene melamine. Bone marrow from the femur was aspirated into a syringe containing fetal calf serum Bone marrow preparations were stained and 1000 polychromatic erythrocytes were scored for the presence of micronuclei. Micronucleased normocytes were also scored.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0 and 48 hours. At 540 mg/kg, males, 7/5000 and females, 6/5000. Controls; males, 4/5000 and females, 6/5000
Genotoxic effects	No clastogenic effects
NOEL (C)/ LOEL (C)	540 uL/kg (498 mg/kg)
Appropriate statistical evaluations	One-way analysis of variance and Duncan's multiple range test
Remarks for results	
Conclusion remarks	Under conditions of the study, 3,5,5-trimethylcyclohexenone is not clastogenic.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	O'Donoghue J.L., Haworth S.R., Curren R.D., Kirby P.E., Lawlor T., Moran E.J., Phillips R.D., Putnam D.L., Rogers-Back A.M., Slesinski R.S., and Thilagar A. (1988) Mutagenicity

	studies on ketone solvents: Methyl ethyl ketone, methyl isobutyl ketone, and i
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data for structurally related ketone, 3,5,5-trimethylcyclohexenone, 97.2%, chemical assay.
Method/guideline	Drosophila mutagenicity assay
Test Type	Drosophila mutagenicity assay
GLP	Yes
Year	1994
Species/Strain	Drosophila melanogaster/Basc females
Sex	Male and Female
Route of administration	Injection
Doses/concentration levels	0 or 12,500 mg/kg
Exposure period	72 hours
Remarks for test conditions	Two to three discs were saturated with the test substance in 5% sucrose solution. Solutions were renewed at 24 and 48 hr. After 72 hrs surviving males were mated. Each male was mated with three Basc virgin females every two to three days to three broods. No more than 100 F1 females were mater over the three broods with P1 males. F2 cultures were scored as presumptive lethals if the number of wild-type males was 0, 1, or less than 5% of the number of Basc males. All putative lethals were confirmed through an additional generation. If the feeding test was nonmutagenic, 2-3 day old CantorS males were injected with 0.7% saline solution containing the test substance.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Lethals for Broods 1,2, and 3: At 12500 mg/kg; 0/2282, 10/1837, and 2/1445. At 0 mg/kg, 0/1855, 8/2013, and 2/1887. % Lethals at 2000 and mg/kg: 0.22% and 0.17%
Genotoxic effects	No mutagenic effects
NOEL (C)/ LOEL (C)	12,500 mg/kg
Appropriate statistical evaluations	Yes (Kasenbaum and Bowen, 1970)
Remarks for results	Under conditions of the test, 3,5,5-trimethylcyclohexenone is not mutageni.c
Conclusion remarks	Under conditions of the test, 3,5,5-trimethylcyclohexenone is not mutageni.c
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability	Code 1. Guideline study.
References	Foureman P., Mason J.M., Valencia R. and Zimmering S. (1994) Chemical Mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. Environmental and Molecular Mutagenesis 23, 208-227.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data for structurally related ketone, 3,5,5-trimethylcyclohexenone, 97.2%, chemical assay.
Method/guideline	Drosophila mutagenicity assay
Test Type	Drosophila mutagenicity assay
GLP	Yes
Year	1994
Species/Strain	Drosophila melanogaster/Basc females
Sex	Male and Female
Route of administration	Oral-Diet
Doses/concentration levels	0 or 2000 mg/kg
Exposure period	72 hours
Remarks for test conditions	Two to three discs were saturated with the test substance in 5% sucrose solution. Solutions were renewed at 24 and 48 hr. After 72 hrs surviving males were mated. Each male was mated with three Basc virgin females every two to three days to three broods. No more than 100 F1 females were mater over the three broods with P1 males. F2 cultures were scored as presumptive lethals if the number of wild-type males was 0, 1, or less than 5% of the number of Basc males. All putative lethals were confirmed through an additional generation. If the feeding test was nonmutagenic, 2-3 day old CantorS males were injected with 0.7% saline solution containing the test substance.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Lethals for Broods 1,2, and 3: At 2000 mg/kg; 1/2281, 4/2077, and 2/2185. At 0 mg/kg, 4/2184, 4/1852, and 3/2087. % Lethals at 2000 and) mg/kg: 0.11% and 0.18%
Genotoxic effects	No mutagenic effects
NOEL (C)/ LOEL (C)	2000 mg/kg
Appropriate statistical evaluations	Yes (Kasenbaum and Bowen, 1970)
Remarks for results	Under conditions of the test, 3,5,5-trimethylcyclohexenone is not mutagenic

Conclusion remarks	Under conditions of the test, 3,5,5-trimethylcyclohexenone is not mutagenic
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Foureman P., Mason J.M., Valencia R. and Zimmering S. (1994) Chemical Mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. Environmental and Molecular Mutagenesis 23, 208-227.
CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related alkyl-substituted cycloalkanone, 2-hexylidenecyclopentanone.
Method/guideline	Micronucleus test (Schmid, 1976)
Test Type	Clastogenicity assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of administration	Intraperitoneal
Doses/concentration levels	
Exposure period	
Remarks for test conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 333, 666, or 1,000 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 500, 333, and 180 mg/kg bw was 2.0, 2.0, 1.9, and 1.2, respectively.
Genotoxic effects	None
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Remarks for results	The test substance did not induce micronuclei in this assay.
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.
CAS	13395-76-1
Substance Name	2,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related alkyl-substituted cycloalkanone, 2-hexylidenecyclopentanone.
Method/guideline	Sex linked recessive lethal mutation assay (Wuergler et al., 1977)
Test Type	Sex-linked lethal assay
GLP	Ambiguous
Year	1983
Species/Strain	Drosophila melanogaster
Sex	Not reported
Route of administration	Oral-Diet
Doses/concentration levels	5mM
Exposure period	
Remarks for test conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Further details of the methodology were not reported.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	No (%) of sex-linked lethals/chromosomes tested: Brood 1, 4/1191 (0.34%); Brood 2 , 3/1112 (0.27%);Brood 3, 3/1201 (0.25%); Controls: Brood 1, 0.23%; Brood 2, 0.19%; Brood 3, 0.29%
Genotoxic effects	
NOEL (C)/ LOEL (C)	5 mM
Appropriate statistical evaluations	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Remarks for results	The test substance did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion remarks	The test substance did not induce sex linked recessive lethals in Drosophila melanogaster.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report

	which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related alkyl-substituted cyclohexanone, tetramethylethylcyclohexanone.
Method/guideline	Micronucleus test (Schmid, 1976)
Test Type	Clastogenicity assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of administration	Intraperitoneal
Doses/concentration levels	
Exposure period	
Remarks for test conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 333, 666, or 1,000 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976).
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The mean number of micronucleated PE/1000 PE at 0, 450, 307, and 180 mg/kg bw was 1.3, 1.3, 1.5, and 1.3, respectively.
Genotoxic effects	None
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Remarks for results	The test substance did not induce micronuclei in this assay.
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem

Toxicol., 21(6), 707-719.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related alkyl-substituted cyclohexanone, tetramethylethylcyclohexanone.
Method/guideline	Sex linked recessive lethal mutation assay (Wuergler et al., 1977)
Test Type	Sex-linked lethal assay
GLP	Ambiguous
Year	1983
Species/Strain	Drosophila melanogaster
Sex	Not reported
Route of administration	Oral-Diet
Doses/concentration levels	10mM
Exposure period	
Remarks for test conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Further details of the methodology were not reported.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	No (%) of sex-linked lethals/chromosomes tested: Brood 1, 3/1218 (0.25%); Brood 2 , 1/1220 (0.08%);Brood 3, 3/1221 (0.25%); Controls: Brood 1, 0.23%; Brood 2, 0.19%; Brood 3, 0.29%
Genotoxic effects	
NOEL (C)/ LOEL (C)	10 mM
Appropriate statistical evaluations	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Remarks for results	The test substance did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion remarks	The test substance did not induce sex linked recessive lethals in Drosophila melanogaster.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. Fd Chem Toxicol., 21(6), 707-719.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexyl alcohol, 2-isopropyl-5-methylcyclohexanol (dl-menthol).
Method/guideline	
Test Type	Dominant lethal assay-Acute study
GLP	No
Year	1975
Species/Strain	Rat/Random bred
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 500 or 3000 mg/kg bw
Exposure period	Single dose
Remarks for test conditions	Groups of male rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 3000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2). Male rats were mated with 2 female rats per week for 8 weeks. 14 days after ma
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	Under conditions of the study, cyclohexyl alcohol, 2-isopropyl-5-methylcyclohexanol (dl-menthol), produced no evidence of genotoxic effects.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexyl alcohol, 2-isopropyl-5-methylcyclohexanol (dl-menthol).
Method/guideline	Chromosomal aberration
Test Type	Cytogenetic assay-Subacute study
GLP	No
Year	1975
Species/Strain	Rat/Albino
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 1150 mg/kg bw
Exposure period	Five doses 24 hours apart
Remarks for test conditions	Groups of rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 3000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) and groups of rats were killed at 6, 24 and 48 hours. 4 hours after administration and 2 hours prior to termination, rats were intraperitoneally injected with 4 mg colcemid/kg bw. Bone marrow was removed and slides were prepared and analyzed.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	None
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	2-Isopropyl-5-methylcyclohexanol did not induce chromosomal aberrations.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

CAS 2816-57-1

Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexyl alcohol, 2-isopropyl-5-methylcyclohexanol (dl-menthol).
Method/guideline	Chromosomal aberration
Test Type	Cytogenetic assay-Acute study
GLP	No
Year	1975
Species/Strain	Rat/Albino
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 500 or 3000 mg/kg bw
Exposure period	6, 24 or 48 hours
Remarks for test conditions	Groups of rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 3000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) and groups of rats were killed at 6, 24 and 48 hours. 4 hours after administration and 2 hours prior to termination, rats were intraperitoneally injected with 4 mg colcemid/kg bw. Bone marrow was removed and slides were prepared and analyzed.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	None.
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	2-Isopropyl-5-methylcyclohexanol did not induce chromosomal aberrations.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone

Remarks for Substance	Data are for structurally related cyclohexyl alcohol, 2-isopropyl-5-methylcyclohexanol (dl-menthol).
Method/guideline	
Test Type	Host-mediated-Subcute study
GLP	No
Year	1975
Species/Strain	Mouse/ICR
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	Test 1: 1.45, 14.5 and 145 mg/kg bw; Test 2:1150 mg/kg bw
Exposure period	Five doses 24 hours apart
Remarks for test conditions	Indicator organisms were Salmonella typhimurium strains G46 and TA1530, and Saccharomyces cervisiae D3. Groups of mice were given 1.45, 14.5 and 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 5000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) by gavage followed by intraperitoneal injection of 2 ml indicator organism. Three hours later, mice were killed and intraperitoneally injected with 2 ml of sterile saline. As much fluid as possible was removed from the peritoneal cavity and dilutions were made from each exudate. Dilutions were plated and incubated for 18-40 hours. Further dilutions were made, plated and incubated at 30deg C for 40 hours after which bacterial scoring was conducted for calculation of mutation frequency and recombinant frequency.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	Elevated recombinant frequency in Saccharomyces D3
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	No significant increase in mutant and recombinant frequency at any dose in Salmonella G46 and TA1530, but in Saccharomyces D3 an elevation of recombinant frequency was reported. In vitro tests using same organisms were all negative.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-

444 (FDA 71-268).

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexyl alcohol, 2-isopropyl-5-methylcyclohexanol (dl-menthol).
Method/guideline	
Test Type	Host-mediated-Acute study
GLP	No
Year	1975
Species/Strain	Mouse/ICR
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	Test 1: 1.45, 14.5 and 145 mg/kg bw; Test 2: 500 and 5000 mg/kg bw
Exposure period	Single exposure
Remarks for test conditions	Indicator organisms were Salmonella typhimurium strains G46 and TA1530, and Saccharomyces cervisiae D3. Groups of mice were given 1.45, 14.5 and 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 5000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) by gavage followed by intraperitoneal injection of 2 ml indicator organism. Three hours later, mice were killed and intraperitoneally injected with 2 ml of sterile saline. As much fluid as possible was removed from the peritoneal cavity and dilutions were made from each exudate. Dilutions were plated and incubated for 18-40 hours. Further dilutions were made, plated and incubated at 30deg C for 40 hours after which bacterial scoring was conducted for calculation of mutation frequency and recombinant frequency.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	Only at 5000 mg/kg bw in Salmonella TA1530.
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	
Remarks for results	In vitro tests using same organisms were all negative.
Conclusion remarks	No significant increase in mutant and recombinant frequency at any dose in Salmonella G46 and Saccharomyces D3. At the highest dose tested in Salmonella TA1530 a significant

	increase in mutant frequency was reported.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexyl alcohol, 2-isopropyl-5-methylcyclohexanol (dl-menthol).
Method/guideline	
Test Type	Micronucleus test
GLP	Ambiguous
Year	1993
Species/Strain	Mouse/B6C3F1
Sex	Male
Route of administration	Intraperitoneal
Doses/concentration levels	0, 250, 500, and 1,000 mg/kg bw
Exposure period	3 daily exposures
Remarks for test conditions	Groups of 5-6 mice were intraperitoneally injected on 3 consecutive days with 1X, 0.5X and 0.25X of the test chemical. A positive control and solvent control were also used. 24 hours after the last treatment, mice were killed, bone marrow removed and slides were prepared. For each mouse, the number of MN-PCE in 2,000 PCE and the percent PCE in 200 erythrocytes were determined.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	0 mg/kg bw: survival=5/5 mice; MN-PCE/1000=2.90; %PCE=54.4 250 mg/kg bw: survival=5/5 mice; MN-PCE/1000=3.60; %PCE=64.2 500 mg/kg bw: survival=5/5 mice; MN-PCE/1000=2.20; %PCE=56.7 1000 mg/kg bw: survival=3/6 mice; MN-PCE/1000=3.67; %PCE=51.8
Genotoxic effects	None
NOEL (C)/ LOEL (C)	
Appropriate statistical evaluations	Yes.

Remarks for results	
Conclusion remarks	2-Isopropyl-5-methylcyclohexanol was negative in the micronucleus test.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions. Part of NTP study program.
References	Shelby, M.D., Erexson, G.L., Hook, G.J., and Tice, R.R. (1993) Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environ Mol Mutagen 21:160-179.

4.3 Repeated Dose Toxicity

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	
Method/guideline	3-week gavage study
GLP	No
Year	1979
Species/Strain	Rat/Charles River CD
Sex	Male and Female
Route of administration	Oral-Gavage
Doses/concentration levels	0, 1000, 2000, or 4000 mg/kg
Exposure period	3 weeks
Frequency of treatment	5 days/week for 3 weeks
Control Group	Yes
Post exposure observation period	None
Remarks for test conditions	Groups of 3 Charles River CD, COBS male rats were administered 2-nonanone (i.e., methyl heptyl ketone) via gavage, 5 days per week for 3 weeks at doses of 1000, 2000, or 4000 mg/kg bw. Individual body weights and feed consumption were recorded on days 0, 3, 7, 14 and 20 of

	treatment. All animals were observed daily for clinical signs of toxicity. Necropsy was performed on all test animals, and tissues were collected for histological examination.
NOAEL(NOEL)	1000 mg/kg
LOAEL(LOEL)	2000 mg/kg
Actual dose received by dose level and sex	
Toxic response/effects by dose level	
Appropriate statistical evaluations	
Remarks for results	Upon necropsy, no gross compound-related changes were detected at any dose level. Histological examination revealed compound related changes in the stomach and liver at the 2000 and 4000 mg/kg bw/d levels, and in the lungs, kidneys, bladder, adrenal glands, bone marrow, brain, and mesenteric fat at the 4000 mg/kg bw/d level. However, it was not reported whether or not these effects were statistically significant. In the stomach, hyperplasia of the epithelium of the non-glandular mucosa was observed with at varying degrees, which were thought to reflect the amount of contact the test material had with the epithelium and the selection of the tissue specimens for examination. Liver changes were characterized by hepatocyte hypertrophy. In the 4000 mg/kg bw/d group, lungs showed minor acute bronchitis and congestion, edema, and atelectasis; the urinary system had dilatation of the lumena of the renal tubules and multiple hemorrrhages in the bladder (1 rat); the adrenal gland was congested; bone marrow and brains were congested in 2 or 3 rats, respectively; and atrophy of the mesenteric adipose tissue occurred in 1 rat. In the 1000 mg/kg test group, no gross or histopathologic compound-related changes were identified.
Conclusion remarks	The 3-week NOAEL for 2-nonanone in rats is 1000 mg/kg
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Krasavage, W.J., and O'Donoghue, J.L. (1979) Repeated oral administration of five ketones and n-heptane to rats. Unpublished report.
CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Assay: 72.3 %
Method/guideline	90 day repeat dose study
GLP	No

Year	1980
Species/Strain	Rat/Charles River CD
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	2000mg/kg
Exposure period	90 days
Frequency of treatment	5 days/week
Control Group	Received tap water at a dose of 4000 mg/kg
Post exposure observation period	
Remarks for test conditions	Groups of Charles River CD male rats (8 per group) were administered the test compound undiluted, by gavage 5 days weekly for 90 days. Animals were housed individually and received rodent laboratory chow and tap water ad libitum. Individual body weights and food consumption were determined twice weekly. All animals were observed daily for clinical signs of toxicity. Animals dying during study were autopsied and tissue sample were collected for histopathological evaluation. Prior to termination blood was collected from the posterior vena cava and subjected hematological examination and clinical chemistry determinations. After 90 days surviving animals were sacrificed, and liver, kidney, brain, adrenal glands, testes, heart and spleen weights were measured and relative organ weights were calculated. Tissues were fixed in 10% formalin, embedded in paraffin, stained with hematoxylin/eosin, an examined microscopically. The tissues evaluated include trachea, lung, thymus, heart, tongue, esophagus, stomach, small intestines, large intestines, liver, kidneys, urinary bladder, adrenal glands, pancreas, thyroids, parathyroids, testis, epididymis, spleen, mesenteric lymph nodes, bone marrow, brain (medulla oblongata, cerebellum and cerebral cortex with thalamus and basal ganglia), spinal chord, sciatic-tibia nerves and dorsal root ganglia.
NOAEL(NOEL)	
LOAEL(LOEL)	2000 mg/kg
Actual dose received by dose level and sex	2000mg/kg
Toxic response/effects by dose level	Hind limb weakness was in 1 rat at 59 days and slowly progressed to severe weakness over the next 31 days. Of the seven remaining rats 4 exhibited mild hind limb weakness by 90 days and 2 others showed no hind limb weakness at 90 days. Feed consumption was significantly less for the test group compared to the control group. At 90 days mean body weights were significantly less for the test group. Hematological examination and clinical chemistry determination for the test and control groups revealed normal values. Blood samples collected at 90 days revealed detectable levels of 2-nonanone

	and 2-hexanone. Mean absolute liver, kidney, adrenal gland, and testes weights were greater for test group then for the control group. Mean absolute heart, spleen, and brain were significantly less for the test group compared to the control.
Appropriate statistical evaluations	ANOVA, Bartlett's test and Duncan's multiple range
Remarks for results	The substance was tested at the highest level no causing immediate death. Although 2-nonanone does not possess the structural features to produce any significant amount of a neurotoxic gamma diketone such as 2,5-hexanedione, impurities in commercial grade of 2-nonanone may contain ketones capable of metabolizing to gamma diketones. Therefore, the appearance of "giant axonal swelling" neurotoxicity in treated animals at least 59 days may not be due to the presence of 2-nonanone per se.
Conclusion remarks	Under conditions of the study, a daily oral dose level of 2000 mg/kg bw of a commercial grade of 2-nonanone was inherently toxic to rats inherent.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods.
References	O'Donohogue J. L. and Krasavage W. J. (1980) 90-Day repeated oral administration of five ketones and n-heptane to rats. Private communication to FEMA. Unpublished Report.
CAS	4485-09-0
Substance Name	4-Nonanone
Remarks for Substance	Data are for isomer, 2,6-dimethyl-4-heptanone, 67%.
Method/guideline	
GLP	Yes
Year	1980
Species/Strain	Rat/Charles River CD
Sex	Male and Female
Route of administration	Oral-Gavage
Doses/concentration levels	0 and 2000 mg/kg
Exposure period	90 days
Frequency of treatment	Daily
Control Group	Yes
Post exposure observation period	None

Remarks for test conditions	2,6-Dimethyl-4-heptanone (67.0% purity; i.e., diisobutyl ketone) was administered to 8 male Charles River rats by gavage for 90 days at a dose of 0 or 2000 mg/kg bw/day. Following the dosing period, liver, kidney, brain, adrenal glands, testes, heart and spleen weights were recorded and relative organ weights calculated. Hematology and clinical chemistry was performed and results were comparable to controls. At necropsy organ weights were measure and a wide variety of tissues were subjected to histopathological examination.
NOAEL(NOEL)	
LOAEL(LOEL)	2000 mg/kg
Actual dose received by dose level and sex	
Toxic response/effects by dose level	
Appropriate statistical evaluations	
Remarks for results	Absolute and relative liver weights, relative kidney weights, and absolute and relative adrenal gland weights were statistically greater than controls. Absolute but not relative brain and heart weights were significantly depressed. All other organ weights were comparable to controls. No compound related gross pathologic changes were identified. Histopathology examinations were also conducted on the test animals and revealed compound related changes in the stomach, liver, and kidneys. In the stomach, all animals showed hyperkeratosis or hyperkeratosis with pseudoepitheliomatous hyperplasia associated with irritation from direct contact by the solvent. In the liver, minor or moderate hepatocyte hypertrophy was observed. In the kidney, hyaline droplet formation was present in the proximal tubular epithelium suggesting alpha-microglobulin-type neuropathy. There was also a minor occurrence of regenerating tubular epithelium and tubular dilation with casts.
Conclusion remarks	Under conditions of the study, 2000 mg/kg of 2,6-dimethyl-4-heptanone administered by gavage was toxic to both male and female rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	O'Donohogue J. L. and Krasavage W. J. (1980) 90-Day repeated oral administration of five ketones and n-heptane to rats. Private communication to FEMA. Unpublished Report.
CAS	821-55-6
Substance Name	5-Nonanone
Remarks for Substance	Assay:98.25%

Method/guideline	90 day repeat dose study
GLP	No
Year	1982
Species/Strain	Rat/Charles River CD
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	233 mg/kg
Exposure period	90 days
Frequency of treatment	5 days/week
Control Group	Received tap water at a dose of 4000 mg/kg
Post exposure observation period	
Remarks for test conditions	Groups of Charles River CD male rats (5 per group) were administered the test compound undiluted, by gavage 5 days weekly for 90 days. Animals were housed individually and received rodent laboratory chow and tap water ad libitum. Individual body weights and food consumption were determined twice weekly. All animals were observed daily for clinical signs of toxicity. Animals dying during study were autopsied and tissue sample were collected for histopathological evaluation. Prior to termination blood was collected from the posterior vena cava and subjected hematological examination and clinical chemistry determinations. After 90 days surviving animals were sacrificed, and liver, kidney, brain, adrenal glands, testes, heart and spleen weights were measured and relative organ weights were calculated. Tissues were fixed in 10% formalin, embedded in paraffin, stained with hematoxylin/eosin, an examined microscopically. The tissues evaluated include trachea, lung, thymus, heart, tongue, esophagus, stomach, small intestines, large intestines, liver, kidneys, urinary bladder, adrenal glands, pancreas, thyroids, parathyroids, testis, epididymis, spleen, mesenteric lymph nodes, bone marrow, brain (medulla oblongata, cerebellum and cerebral cortex with thalamus and basal ganglia), spinal chord, sciatic-tibia nerves and dorsal root ganglia.
NOAEL(NOEL)	233 mg/kg
LOAEL(LOEL)	
Actual dose received by dose level and sex	
Toxic response/effects by dose level	At study termination, both body weights and food consumption were not statistically significant from the control group. Necropsy findings were unremarkable. No giant axonal swelling was observed, although slight neuropathologic changes were observed (myelin ovoid formation, remyelination or adaxonal

	myelin in 3 of 5 rats.
Appropriate statistical evaluations	ANOVA, Bartlett's test and Duncan's multiple range
Remarks for results	The study was designed to screen for ketone neurotoxicity. Dose levels of 1000 mg/kg of 5-nonanone have been shown to produce clear evidence of "giant axonal swelling" neurotoxicity. Doses below 200 mg/kg are not expected to produce any such neurotoxic effects.
Conclusion remarks	Under conditions of the study, a daily oral dose level of 233 mg/kg bw of 5-nonanone was not inherently toxic to rats inherent
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	O'Donohogue J. L. and Krasavage W. J., DiVencenzo G. and Ziegler D.(1982) Commercial grade methyl heptyl ketone (5-methyl-2-octanone) neurotoxicity: Contribution of 5-nonanone.Toxiclogy and Applied Pharmacology, 62, 307-316.
CAS	33083-83-9
Substance Name	5-Undecanone
Remarks for Substance	Data for isomeric ketone, 2,8-dimethyl-5-nonanone. Assay: 99.2 %.
Method/guideline	90 day repeat dose study
GLP	No
Year	1980
Species/Strain	Rat/Charles River CD
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	4000mg/kg
Exposure period	90 days
Frequency of treatment	5 days/week
Control Group	Received tap water at a dose of 4000 mg/kg
Post exposure observation period	
Remarks for test conditions	Groups of Charles River CD male rats (8 per group) were administered the test compound undiluted, by gavage 5 days weekly for 90 days. Animals were housed individually and received rodent laboratory chow and tap water ad libitum. Individual body weights and food consumption were determined

	twice weekly. All animals were observed daily for clinical signs of toxicity. Animals dying during study were autopsied and tissue sample were collected for histopathological evaluation. Prior to termination blood was collected from the posterior vena cava and subjected hematological examination and clinical chemistry determinations. After 90 days surviving animals were sacrificed, and liver, kidney, brain, adrenal glands, testes, heart and spleen weights were measured and relative organ weights were calculated. Tissues were fixed in 10% formalin, embedded in paraffin, stained with hematoxylin/eosin, an examined microscopically. The tissues evaluated include trachea, lung, thymus, heart, tongue, esophagus, stomach, small intestines, large intestines, liver, kidneys, urinary bladder, adrenal glands, pancreas, thyroids, parathyroids, testis, epididymis, spleen, mesenteric lymph nodes, bone marrow, brain (medulla oblongata, cerebellum and cerebral cortex with thalamus and basal ganglia), spinal chord, sciatic-tibia nerves and dorsal root ganglia.
NOAEL(NOEL)	
LOAEL(LOEL)	4000 mg/kg
Actual dose received by dose level and sex	4000 mg/kg
Toxic response/effects by dose level	Two of the 8 animals died by day 3. The test group showed a 17% decrease in food consumption during the first week of treatment. Body weights were also reduced. However, at study termination both body weights and food consumption were not statistically significant from the control group. Blood leukocyte counts were lower for the test group and ASAT and ALT enzyme activities were elevated. The latter changes were not accompanied by any evidence of histopathology. Mean absolute and relative kidney, adrenal, testes, and liver weights were increased for the test group. Histopathological examination revealed hepatocyte hypertrophy and renal hydraline droplet formation, probably the result of alpha-2-microglobulin formation.
Appropriate statistical evaluations	ANOVA, Bartlett's test and Duncan's multiple range
Remarks for results	The substance was tested at or near the acute oral LD50. The study was designed to screen for ketone neurotoxicity.
Conclusion remarks	Under conditions of the study, a daily oral dose level of 4000 mg/kg bw of 2,8-dimethyl-5-nonanone was inherently toxic to rats.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods.
References	O'Donohogue J. L. and Krasavage W. J. (1980) 90-Day repeated oral administration of five ketones and n-heptane to rats. Private communication to FEMA. Unpublished Report.

CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexanone derivative, 3,5,5-trimethylcyclohexenone.
Method/guideline	2-yr NTP Bioassay
GLP	Yes
Year	1986
Species/Strain	Rat/Fischer 344/N
Sex	Male and Female
Route of administration	Oral-Gavage
Doses/concentration levels	0, 250, or 500 mg/kg
Exposure period	103 weeks
Frequency of treatment	5 days per week
Control Group	Yes. Received corn oil vehicle only
Post exposure observation period	
Remarks for test conditions	In a two-year study dose levels of 0, 250 or 500 mg/kg bw per day of 3,5,5-trimethylcycloheneone were given to groups of F344/N rats (50/sex/group) by gavage in corn oil 5 days a week daily for 103 weeks (NTP, 1986; Bucher et al., 1986). Food and water were provided ad libitum. Moribund animals were euthanized. Weights were recorded weekly and at the termination of the experiment survivors were sacrificed and necropsies performed.
NOAEL(NOEL)	
LOAEL(LOEL)	250 mg/kg
Actual dose received by dose level and sex	
Toxic response/effects by dose level	Gavage errors accounted for a significant number of deaths (36/300) in both male and female rats. Nephropathy was noted in both test and control rats of both sexes after natural death or at termination. In test animals, increased incidence of mineral deposits in renal collecting ducts (31/50,62% and 20/50, 40%), and tubular cell hyperplasia (1/50, 2% and 4/50, 8%), adenomas (0/50 and 2/50, 8%), and adenocarcinomas (3/50, 6% and 1/50, 2%) were observed in male rats at 250 mg/kg bw per day and 500 mg/kg bw per day, respectively but not in female rats (See Table A3). Tubule mineralization was characterized by basophilic aggregates found in the medullary collecting ducts, often occurring coincidentally with lesions of chronic nephropathy.

Appropriate statistical evaluations	Yes
Remarks for results	
Conclusion remarks	Under conditions of these 2-year gavage studies, there is some evidence of carcinogenicity of 3,5,5-trimethylcycloheneone in the male F344/N rat as shown by the occurrence of renal tubular cell adenomas and adenocarcinomas in animals given 250 or 500 mg/kg/day.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Bucher J.R., Huff J., and Kluwe W.M. (1986) Toxicology and carcinogenesis studies of isophorone in F344 rats and B6C3F1 mice. Toxicology. 39(2), 207-219.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related substance, 2-isopropyl-5-methylcyclohexanol (dl-menthol).
Method/guideline	Carcinogenicity study
GLP	No
Year	1979
Species/Strain	Mouse/B6C3F1
Sex	Male and Female
Route of administration	Oral-Diet
Doses/concentration levels	0, 2,000 or 4,000 ppm (0, 300 or 600 mg/kg bw, respectively)
Exposure period	103 weeks
Frequency of treatment	Daily
Control Group	Basal diet with 2% corn oil
Post exposure observation period	1 week
Remarks for test conditions	A carcinogenicity study was conducted in which groups of 50 B6C3F1 mice of each sex were administered 0, 2,000 or 4,000 ppm dl-2-isopropy-5-methylcyclohexanol in their feed daily for 103 weeks. Dietary concentrations were calculated to provide corresponding average daily intake levels of 0, 300 or 600 mg/kg bw, respectively. Animals were housed five per cage and were observed twice daily for signs of toxicity. Body weights and food consumption were recorded every two weeks for the first twelve weeks, and once a month thereafter. Necropsies and histological examinations were performed on all animals at

	the termination of the study and on those found dead during the study.
NOAEL(NOEL)	300 mg/kg bw/day
LOAEL(LOEL)	600 mg/kg bw/day
Actual dose received by dose level and sex	
Toxic response/effects by dose level	The mean body weights of the male and female mice administered 300 or 600 mg dl-2-isopropy-5-methylcyclohexanol/kg bw were slightly lower when compared to the controls. Survival of the high- and low-dose groups of male mice was similar to the vehicle control animals (controls, 32/50; low-dose, 32/50; high-dose, 35/50). Survival of the high-dose group of female mice was significantly less than that of the control animals (controls, 36/50; high-dose, 45/50). However, decreased survival was not accompanied by any evidence of toxicity in the high-dose group. Survival of the low-dose female mice was similar to the control animals (controls, 36/50; low-dose, 40/50). An increase in the incidence of hepatocellular carcinomas was observed in high-dose male mice (controls, 8/47; low-dose, 8/49; high-dose, 14/48), but was not statistically different from that observed historically in mice of that age and strain [Haseman et al., 1986]. A low incidence of alveolar/bronchiolar adenomas of the lung was observed in both the low- and high-dose females but was not statistically different from the incidence of this neoplasm in historical control groups. Under the conditions of this study, it was concluded that dl-2-isopropy-5-methylcyclohexanol was not carcinogenic and did not produce any organ-specific toxicity for either sex of B6C3F1 mice at dose levels of 300 or 600 mg/kg bw.
Appropriate statistical evaluations	Yes.
Remarks for results	NOAEL based on decreased survival in female mice.
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexanone derivative 2-Isopropyl-5-methylcyclohexanol.
Method/guideline	Carcinogenicity study

GLP	No
Year	1979
Species/Strain	Rat/F344
Sex	Male and Female
Route of administration	Oral-Diet
Doses/concentration levels	0, 3750, or 7500 ppm (~0, 187 or 375 mg/kg bw, respectively)
Exposure period	103 weeks
Frequency of treatment	Daily
Control Group	Basal diet with 2% corn oil
Post exposure observation period	2 weeks
Remarks for test conditions	Groups of 50 Fischer 344 rats of each sex were administered 0, 3750 or 7500 ppm dl-2-isopropy-5-methylcyclohexanol in their feed daily for 103 weeks. Dietary concentrations were calculated to provide corresponding average daily intake levels of approximately 0, 187 or 375 mg/kg bw, respectively. Animals were housed five per cage until week 48 when the male rats were divided into groups of two to three per cage. The animals were observed twice daily for signs of toxicity. Body weight and food consumption were recorded every two weeks for the first twelve weeks, and once a month thereafter. Necropsies and histological examinations were performed on all animals at the termination of the study and on those found dead during the study.
NOAEL(NOEL)	375 mg/kg bw/day
LOAEL(LOEL)	
Actual dose received by dose level and sex	
Toxic response/effects by dose level	The mean body weights of the male and female rats administered 187 or 375 mg/kg dl-menthol were slightly lower when compared to the controls. Survival of the high- and low-dose groups of male (controls, 31/50; low-dose, 33/50; high-dose, 34/50) and female (controls, 36/50; low-dose, 35/50; high-dose, 38/50) rats was similar to the control animals. Chronic inflammation of the kidney observed in the dosed older males was not considered by the authors to be related to the administration of dl-2-isopropy-5-methylcyclohexanol since the effect is commonly observed in aged male Fischer 344 rats. There was no increase in the incidence of neoplasms of dosed females compared to that of control animals. In the low-dose (10/49) and high-dose (7/49) female groups, fibroadenomas of the mammary glands occurred at a lower incidence than in the control group (20/50). Alveolar/bronchiolar adenomas or carcinomas were reported only for the female control rats. Under the conditions of this study, it was concluded that dl-2-isopropy-5-methylcyclohexanol was neither carcinogenic nor

	toxic for either sex of Fischer 344 rats at dose levels of 187 or 375 mg dl-2-isopropy-5-methylcyclohexanol /kg bw.
Appropriate statistical evaluations	Yes.
Remarks for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexanone derivative 2-Isopropyl-5-methylcyclohexanol.
Method/guideline	90-day toxicity study
GLP	No
Year	1979
Species/Strain	Rat/F344
Sex	Male and Female
Route of administration	Oral-Diet
Doses/concentration levels	0, 930, 1870, 3750, 7500, or 15000 ppm (~0, 93, 187, 375, 750 or 1500 mg dl-2-isopropy-5-methylcyclohexanol/kg bw/day)
Exposure period	13 weeks
Frequency of treatment	Daily
Control Group	Basal diet with 2% corn oil
Post exposure observation period	
Remarks for test conditions	Groups of 10 female and 10 male Fischer 344 rats per group were maintained on diets containing dl-menthol at concentrations of 0, 930, 1870, 3750, 7500, or 15000 ppm for 13 weeks. Dietary concentrations were calculated to provide corresponding average daily intake levels of 0, 93, 187, 375, 750 or 1500 mg dl-2-isopropy-5-methylcyclohexanol/kg bw, respectively. Necropsies were performed on all animals at the end of the study. Histopathological examination was performed on tissues from the control animals, the highest dose group, and selected tissues from the second highest dose group.

NOAEL(NOEL)	750 mg/kg bw/day
LOAEL(LOEL)	1500 mg/kg bw/day
Actual dose received by dose level and sex	
Toxic response/effects by dose level	Final mean body weights of the male and female rats at all dose levels were similar to those of the controls. A slight increase in the incidence of interstitial nephritis was observed in high-dose male rats. No adverse effects were reported for male or female rats administered 93, 187, 375, or 750 mg dl-2-isopropy-5-methylcyclohexanol/kg bw/day.
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related cyclohexanone derivative 2-Isopropyl-5-methylcyclohexanol.
Method/guideline	90-day toxicity study
GLP	No
Year	1979
Species/Strain	Mouse/B6C3F1
Sex	Male and Female
Route of administration	Oral-Diet
Doses/concentration levels	0, 930, 1870, 3750, 7500, or 15000 ppm (~0, 140, 281, 563, 1125 or 2250 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw/day)
Exposure period	13 weeks
Frequency of treatment	Daily
Control Group	Basal diet with 2% corn oil
Post exposure observation	

period	
Remarks for test conditions	Groups of 10 male and 10 female B6C3F1 mice were maintained on diets containing dl-2-isopropyl-5-methylcyclohexanol at dietary concentrations of 0, 930, 1870, 3750, 7500, or 15000 ppm for 13 weeks. Dietary concentrations were calculated to provide average daily intake levels of 0, 140, 281, 563, 1125 or 2250 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw, respectively. Necropsies were performed on all animals at the end of the study. Histopathological examination was performed on tissues from the control animals, the 2250 mg/kg bw/day group, and selected tissues from the 1125 mg/kg bw/day group.
NOAEL(NOEL)	1125 mg/kg bw/day
LOAEL(LOEL)	563 mg/kg bw/day
Actual dose received by dose level and sex	
Toxic response/effects by dose level	Six mice (sex not specified) died during the study but the deaths could not be attributed to compound administration. Final mean body weights of the male mice and female mice were not statistically different from those of the controls except for the high-dose female group which showed statistically significant decreased body weights. A slight increase in the incidence of perivascular lymphoid hyperplasia and interstitial nephritis was reported in the female mice given the two highest dose levels. No adverse effects were reported for male or female mice administered 140, 281 or 563 mg dl-2-isopropy-5-methylcyclohexanol/kg bw/day.
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Data are for mixture of structurally related alkyl-substituted cyclohexanones and cyclohexanols: 1)46.8% (1a, 2ß, 5a)-2-isopropy-5-methylcyclohexanol 2)3.97% (1a, 2a, 5a)-2-isopropy-5-methylcyclohexanol 3)0.86% (1 ß, 2ß, 5a)-2-isopropy-5-methylcyclohex

Method/guideline	28-Day Oral Toxicity Study
GLP	Yes
Year	1990
Species/Strain	Rat/Sprague Dawley
Sex	Male and Female
Route of administration	Oral Gavage
Doses/concentration levels	0, 100, 200, or 400 mg/kg bw
Exposure period	29 or 30
Frequency of treatment	Once daily
Control Group	Yes, vehicle only
Post exposure observation period	
Remarks for test conditions	Groups (10/sex/group) of male and female Sprague-Dawley rats were given daily dose levels of 0, 100, 200, or 400 mg/kg bw of a mixture of alkyl-substituted cyclohexanol by gavage in corn oil (10 ml/kg) daily for 29 or 30 days. Clinical signs were monitored twice weekly and body weights and food consumption were measured weekly. At the initiation of the study, 10 animals were randomly selected from the pool of animals not selected fro the study. They were fasted overnight and blood samples were drawn and analyzed for baseline clinical chemistry and hematology parameters. Prior to termination, animals were injected with ketamine and blood samples were drawn for clinical chemistry and hematology. At necropsy, organ weights (brain, spleen, liver, heart, kidneys, testes with epididymides, adrenals, ovaries, and pituitary) were measured, and tissues (26) were preserved in 10% formalin. All tissues from the control and high-dose groups and tissues from the heart, liver, kidneys, and gross lesions from the low- and mid-dose group were embedded in paraffin, stained with hematoxylin and eosin, and examined microscopically.
NOAEL(NOEL)	Less than 100 mg/kg bw per day for males and 400 mg/kg bw per day for females.
LOAEL(LOEL)	100 mg/kg bw per day (based on appearance of alpha-2-microglobulin effect in males).
Actual dose received by dose level and sex	0, 100, 200, or 400 mg/kg bw
Toxic response/effects by dose level	All animals survived to study termination with high dose males showing increased incidence of urine staining during clinical observations. Except for a non-statistically significant decrease in mean body weigh in high-dose males, there were no statistically significant differences in body weight or food consumption between treated and control groups. A significant decrease in serum glucose levels was reported in the mid- and high-dose males that the authors, in part, attribute to change in nutritional status as revealed by a decreased body weights in

	the high-dose group. A treatment-related increase in alkaline phosphatase was reported in high-dose males. Measurement of body weight, food consumption, hematology and clinical chemistry parameters revealed no significant changes between test and control female rats. There were statistically significant increases in relative kidney weights in high-dose males. Histopathological findings revealed renal tubule protein droplets in all groups of treated male rats. The authors considered these findings related to the lysosomal handling of alpa-2-micro-globulin, a protein specific to the male Sprague-Dawley rat. Absolute and relative liver weights in high-dose females also were significantly increased but these changes were not confirmed by histopathological examination.
Appropriate statistical evaluations	Dunnett's Control versus Treatment Comparison.
Remarks for results	Based exclusively on the renal pathology (alpha-2-microglobulin effect) reported in all dosed groups of male rats, the authors concluded that the no observable adverse effect level (NOAEL) for the mixture is less than 100 mg/kg bw per day in male rats and 400 mg/kg bw per day in female rats.
Conclusion remarks	The NOAEL is less than 100 mg/kg bw in male Sprague-Dawley rats and 400 mg/kg bw per day for female rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Serota D. G. (1990) 28-Day oral toxicity study in rats: B100. HLA Study No. 642-477. Private Communication to FEMA. Unpublished Report.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for structurally related substance 2-hexanone, 5-methyl-, and purity 99.2%.
Method/guideline	
GLP	No
Year	1979
Species/Strain	Rat/Charles River CD
Sex	Male
Route of administration	Oral-Gavage
Doses/concentration levels	0 and 2000 mg/kg
Exposure period	90days

Frequency of treatment	A single daily gavage 5 days/week
Control Group	Yes; treatment with water
Post exposure observation period	None
Remarks for test conditions	This study involved only a single maximum tolerated dose, and was designed to determine the neurotoxicity and subchronic effects of a series of different ketones against that of n-heptane. Body weight and feed consumption was assessed twice weekly. A full complement of tissues was harvested for histopathology with special emphasis placed on the handling and collection of neural tissues. Several tissues were also weighted. Complete hematology and clinical chemistries were also conducted.
NOAEL(NOEL)	Not established.
LOAEL(LOEL)	
Actual dose received by dose level and sex	
Toxic response/effects by dose level	
Appropriate statistical evaluations	Yes, one-way ANOVA
Remarks for results	No evidence of neurotoxicity was seen based on an absence of alterations in appearance or behavior, and histological changes in nervous tissue. Feed intake was, in general, slightly depressed throughout the study and was significantly lower during the first week. Body weights were significantly reduced at essentially all time points. There was no effect on the erythron. Effects noted in the clinical chemistry profile included slight, but statistically significant, increases in SGOT, SGPT and urea nitrogen. Urea nitrogen levels were still within levels seen in historical controls. Absolute and relative increases in liver and adrenal weights were seen. Relative increases were seen in other tissues; however, their significance is negated by a significantly decreased bodyweight. Histological evidence of gastric irritation was manifested by hyperkeratosis, and hyperkeratosis with pseudoepitheliomatuos hyperplasia and submucosal thickening and edema. Liver changes consisted of a diffuse hepatocyte hypertrophy, and microfoci of hyperplasia in some rats. The latter effect was characterized by an increase in cytoplasmic and generally nuclear size. Three types of nodules were present. The first type was identified on the basis of diffuse increase in cytoplamic masophilia, the second type contained heavily vacuolated cells, and the third had very large vesicular nuclei with prominent nucleoli. These types of nodules are generally regarded as pre-neoplastic changes. A few animals also exhibited necrosis of individual hepatocytres, a few others had vacuolation of individual hepatocytes. Some animals also had bile duct epithelial hyperplasia. Renal changes included and increased incidence of regenerating tubular epithelium and dilatation with casts, and hyaline droplet

	formation in the proximal tubular epithelium.
Conclusion remarks	Other than the finding of a diffuse hepatocyte hypertrophy, the observation of microfoci of hyperplasia was not reproduced following inhalation exposure. Inhalation is the most relevant route by which humans are exposed. Peak blood levels at the highest exposure level in the inhalation study were similar to that following oral intubation.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Eastman Kodak Co. (1979) 90-day repeated oral administration of five ketones and n-heptane to rats. Unpublished report.
CAS	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	
Method/guideline	14-day minimum toxicity screen
GLP	Yes
Year	1987
Species/Strain	Rat/Fischer 344
Sex	Male and Female
Route of administration	Oral-Diet
Doses/concentration levels	10 mg/kg
Exposure period	14 days
Frequency of treatment	Continuously in the diet for 14 days
Control Group	Basal diet only
Post exposure observation period	None
Remarks for test conditions	Groups of 5 male and female Fischer 344 rats were maintained on a diet containing 2-pentadecanone in corn oil at levels calculated to provide an average daily intake of 10 mg/kg bw. Control groups received the basal diet and the corn oil vehicle only. Body weight and food consumption were measured weekly. At necropsy on day 14, liver and kidneys were weighed and prepared for histopathology.
NOAEL(NOEL)	10 mg/kg bw
LOAEL(LOEL)	
Actual dose received by dose level and sex	

Toxic response/effects by dose level	No effects were reported.
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	The 14-day NOEL for the administration of 2-pentadecanone in the diet was reported to be 10 mg/kg bw.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Van Miller J.P. and Gill M. W. (1987) 14-day dietary minimum toxicity screen of 4-(2-furyl)-3-buten-2-one, oxotetradecanoic acid glyceride, 3-oxooctanoic acid glyceride, 2-pentadecanone, and o-methoxybenzaldehyde. Unpublished report to FEMA.

4.4 Reproductive Toxicity

CAS	823-55-2
Substance Name	2,4-Dimethylcyclohexanone
Remarks for Substance	Data are for mixture of structurally related alkyl-substituted cyclohexanones and cyclohexanols. 1) 46.8% (1a, 2ß, 5a)-2-isopropy-5-methylcyclohexanol 2) 3.97% (1a, 2a, 5a)-2-isopropy-5-methylcyclohexanol 3) 0.86% (1 ß, 2ß, 5a)-2-isopropy-5-methylcyclo
Method/guideline	*in vivo* Reproductive and Developmental Toxicity Screening Test
Test Type	
GLP	Yes
Year	1989
Species/Strain	Rat/Sprague Dawley
Sex	Female
Route of administration	Oral-Gavage
Duration of test	39 days
Doses/concentration levels	0, 150, 750, or 1,500 mg/kg bw

Premating Exposure period for males	
Premating Exposure period for females	7 days
Frequency of treatment	Daily
Control Group and treatment	Yes, vehicle only (corn oil)
Remarks for test conditions	Groups of ten female rats were orally administered an oil containing a mixture of alkyl-substituted cyclohexanone derivatives via gavage at dose levels of 0, 150, 750 or 1500 mg/kg bw/d for seven days prior to and through cohabitation, gestation, delivery and a four day lactation period. The vehicle was corn oil. Body weights, food consumption and clinical signs were recorded throughout the observation period. All dams were necropsied and examined for gross lesions on Day 25 of presumed gestation for rats not delivering a litter and four days postpartum for rats delivering a litter. Pups delivered were sacrificed on day 4 post partum; any pups dying during the lactation period were necropsied.
NOAEL(NOEL)	150 mg/kg bw
LOAEL(LOEL)	
Actual dose received by dose level and sex	0, 150, 750, or 1,500 mg/kg bw
Parental data and F1 as appropriate	Deaths or moribund sacrifice were reported in 2/10 females at 750 mg/kg bw per day and 5/10 females at 1,500 mg/kg bw per day. Additional clinical observations included decreased motor activity, ataxia, dysnea, rales, chromorrhinorrhea, un-groomed coat and thin appearance at the 750 and 1500mg/kg bw per day dose levels. Urine stained fur and excess salivation were observed at all dose levels. Significant (P < or = 0.05) decreases in body weight and food consumption were reported during the pre-mating period in the 750 and 1500 mg/kg bw per day groups compared to those for control group. A non-statistically significant decrease in maternal body weight gain was reported in the 750 mg/kg bw per day group compared to the control group. The single dam that delivered a litter in the high-dose group also showed less weight gain. Absolute and relative feed consumption were comparable between the low-, mid, and control groups. On day 1 of lactation, the average body weight of dams in the mid-dose group and the single dam in the high-dose group was significantly (P < or =0.01) less than in the control group. During lactation, dams in the mid-dose group gained weight while the weight gain in the single dam in the high-dose group were comparable to that for the control group. Compared to control animals, feed consumption in the mid- and high-dose group decreased significantly (P< or =0.01) during premating but was increased significantly (P< or =0.01 to 0.05) during lactation. Of the rats surviving the cohabitation period 4 of 5 became

	pregnant at the highest dose level (1500 mg/kg bw per day). Live litters were reported for 9/19, 8/10, 5/6, and 1/4 pregnant females in the control, 150, 750, and 1500 mg/kg bw per day groups, respectively. Increased number of dams with stillborn pups, stillborn pups, and late resorptions in utero were reported in the 750 mg/kg bw per day group. At 1500 mg/kg bw per day, 2 rats had only resorptions in utero when found dead on gestation day 23 and one rat possessed only empty implantation sites in utero on day 25 of presumed gestation.
Offspring toxicity F1 and F2	On day 1 postparturition, litters of dams in the 750 and 1500 mg/kg bw per day groups showed non-statistically significant decreases in pup weight which by day 4 were comparable to controls in the mid-dose group, but less than the control value in the high dose group. On day 4 postpaturition, significant (P< or = 0.01) increases in pup mortality were reported in the mid- and high-dose groups compared to controls. However, even at the highest dose level, there was no evidence of an effect of the test article on implantation, duration of gestation, pup sex ratio, or gross morphology of pups.
Appropriate statistical evaluations	Yes
Remarks for results	
Conclusion remarks	Authors concluded that the maternal no adverse effect level (NOAEL) for reproductive effects was 150 mg/kg bw per day and the offspring NOAEL for developmental effects is higher than 150 mg/kg bw per day, but less than 750 mg/kg bw per day.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Hoberman A. M. (1989) Reproductive and developmental toxicity screening of B100 administered orally via gavage to Crl:CD(SD)Br female rats. Argus Research Laboratories, Inc. Protocol 412-015. Private Communication to FEMA. Unpublished Report.
CAS	823-55-2
Substance Name	2,4-Dimethylcyclohexanone
Remarks for Substance	Data are for alkyl-substituted cyclohexanol, 2-Isopropyl-5-methylcyclohexanol
Method/guideline	
Test Type	Dominant lethal assay-Acute study
GLP	No

Year	1975
Species/Strain	Random bred rat
Sex	Male
Route of administration	Oral-Gavage
Duration of test	
Doses/concentration levels	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 500 or 3000 mg/kg bw
Premating Exposure period for males	
Premating Exposure period for females	
Frequency of treatment	Single dose
Control Group and treatment	Saline
Remarks for test conditions	Groups of male rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 3000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2). Male rats were mated with 2 female rats per week for 8 weeks. 14 days after mating, females were killed and the uterus was examined for early deaths, late fetal deaths and total implantations.
NOAEL(NOEL)	
LOAEL(LOEL)	
Actual dose received by dose level and sex	
Parental data and F1 as appropriate	
Offspring toxicity F1 and F2	
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	No effect on early deaths, late fetal deaths and total implantations was reported when 2-isopropyl-5-methylcyclohexanol was administered to male rats prior to mating.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

CAS	823-55-2
Substance Name	2,4-Dimethylcyclohexanone
Remarks for Substance	Data are for alkyl-substituted cyclohexanol, 2-Isopropyl-5-methylcyclohexanol
Method/guideline	
Test Type	Dominant lethal assay- Subacute study
GLP	No
Year	1975
Species/Strain	Random bred rat
Sex	Male
Route of administration	Oral-Gavage
Duration of test	
Doses/concentration levels	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 1150 mg/kg bw
Premating Exposure period for males	
Premating Exposure period for females	
Frequency of treatment	Five doses 24 hours apart
Control Group and treatment	Saline
Remarks for test conditions	Groups of rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 1150 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) for 5 consecutive doses, 24 hours apart. After the last dose, male rats were mated with 2 female rats per week for 7 weeks. Fourteen days after mating, females were killed and the uterus was examined for early deaths, late fetal deaths and total implantations.
NOAEL(NOEL)	
LOAEL(LOEL)	
Actual dose received by dose level and sex	
Parental data and F1 as appropriate	
Offspring toxicity F1 and F2	
Appropriate statistical evaluations	
Remarks for results	
Conclusion remarks	No effect on early deaths, late fetal deaths and total implantations was reported when 2-isopropyl-5-

	methylcyclohexanol was administered to male rats prior to mating.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).
CAS Numerical	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Substance identified by infrared and chemical assay performed by gas chromatography
Method/guideline	Fertility screening assay
Test Type	
GLP	No
Year	1975
Species/Strain	Mice/CF1
Sex	Female
Route of administration	Intraperitoneal
Duration of test	Period of gestation
Doses/concentration levels	50 mg/kg bw/day
Premating Exposure period for males	
Premating Exposure period for females	
Frequency of treatment	Daily
Control Group and treatment	62 untreated CF1 female mice
Remarks for test conditions	A group of 8 female CF1 mice were given 50 mg/kg bw dose of 2-pentadecanone by Intraperitoneal injection daily during gestation. The percent pregnant, number of viable fetuses per litter, number of resorption sites, and dead *in utero* per litter were recorded and expressed as a percent of the control value.
NOAEL(NOEL)	50 mg/kg bw
LOAEL(LOEL)	
Actual dose received by dose level and sex	50 mg/kg bw
Parental data and F1 as	No effect on maternal body weight were observed and no sign

appropriate	of toxicity were recorded. For the test group compared to the control group, 100% pregnancy rate, 0% for the average number of resorption sites per litter and 78% average number of fetuses per litter were reported. A 25% (p=0.05) difference between test and control group was considered significant by the authors. Diethylstilbesterol was used as a positive control (10 ug/kg bw). The positive control showed 0% pregnancy rate, 0% fetuses per litter, and 0% resorption sites per litter.
Offspring toxicity F1 and F2	
Appropriate statistical evaluations?	Yes
Remarks for results	
Conclusion remarks	Under conditions of the experiment, a 50 mg/kg bw dose of 2-pentadecanone given daily by intraperitoneal injection to female rats produced no maternal or reproductive effects.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Carlson G. L., Hall I. H., and Piantadosi (1975) Cycloalkanone. 7. Hypocholesterolemic activity of aliphatic compounds related to 2,8-dibenzylcyclooctanone. Journal of Medicinal Chemistry 18(10), 234-236.
CAS Numerical	2345-28-0
Substance Name	2-Pentadecanone
Remarks for Substance	Structurally related substance 8-pentadecanone, identified by infrared and chemical assay performed by gas chromatography
Method/guideline	Fertility screening assay
Test Type	
GLP	No
Year	1975
Species/Strain	Mice/CF1
Sex	Female
Route of administration	Intraperitoneal
Duration of test	Period of gestation
Doses/concentration levels	50 mg/kg bw/day
Premating Exposure period for males	
Premating Exposure period for females	

Frequency of treatment	Daily
Control Group and treatment	62 untreated CF1 female mice
Remarks for test conditions	A group of 8 female CF1 mice were given 50 mg/kg bw dose of 8-pentadecanone by intraperitoneal injection daily during gestation. The percent pregnant, number of viable fetuses per litter, number of resorption sites, and dead *in utero* per litter were recorded and expressed as a percent of the control value.
NOAEL(NOEL)	50 mg/kg bw
LOAEL(LOEL)	
Actual dose received by dose level and sex	50 mg/kg bw
Parental data and F1 as appropriate	No effect on maternal body weight were observed and no sign of toxicity were recorded. For the test group compared to the control group, 67% pregnancy rate, 0% for the average number of resorption sites per litter and 81% average number of fetuses per litter were reported. A 25% (p=0.05) difference between test and control group was considered significant by the authors. Diethylstilbesterol was used as a positive control (10 ug/kg bw). The positive control showed 0% pregnancy rate, 0% fetuses per litter, and 0% resorption sites per litter.
Offspring toxicity F1 and F2	
Appropriate statistical evaluations?	Yes
Remarks for results	
Conclusion remarks	Under conditions of the experiment, a 50 mg/kg bw dose of 8-pentadecanone given daily by intraperitoneal injection to female rats during gestation exhibited no significant maternal effects and only mild to marginal reproductive effects.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Carlson G. L., Hall I. H., and Piantadosi (1975) Cycloalkanone. 7. Hypocholesterolemic activity of aliphatic compounds related to 2,8-dibenzylcyclooctanone. Journal of Medicinal Chemistry 18(10), 234-236.
CAS Numerical	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Substances identified by infrared and chemical assay performed by gas chromatography
Method/guideline	Fertility screening assay
Test Type	

GLP	No
Year	1975
Species/Strain	Mice/CF1
Sex	Female
Route of administration	Intraperitoneal
Duration of test	Period of gestation
Doses/concentration levels	50 mg/kg bw/day
Premating Exposure period for males	
Premating Exposure period for females	
Frequency of treatment	Daily
Control Group and treatment	62 untreated CF1 female mice
Remarks for test conditions	A group of 8 female CF1 mice were given 50 mg/kg bw dose of 2-undecanone by intraperitoneal injection daily during gestation. The percent pregnant, number of viable fetuses per litter, number of resorption sites, and dead *in utero* per litter were recorded and expressed as a percent of the control value.
NOAEL(NOEL)	50 mg/kg bw
LOAEL(LOEL)	
Actual dose received by dose level and sex	50 mg/kg bw
Parental data and F1 as appropriate	No effect on maternal body weight were observed and no sign of toxicity were recorded. For the test group compared to the control group, 50% pregnancy rate, 0% for the average number of resorption sites per litter and 60% average number of fetuses per litter were reported. A 25% (p=0.05) difference between test and control group was considered significant by the authors. Diethylstilbesterol was used as a positive control (10 ug/kg bw). The positive control showed 0% pregnancy rate, 0% fetuses per litter, and 0% resorption sites per litter.
Offspring toxicity F1 and F2	
Appropriate statistical evaluations?	Yes
Remarks for results	
Conclusion remarks	Under conditions of the experiment, a 50 mg/kg bw dose of 2-undecanone given daily by intraperitoneal injection to female rats during gestation exhibited no significant maternal effects and only mild to marginal reproductive effects.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Carlson G. L., Hall I. H., and Piantadosi (1975) Cycloalkanone. 7. Hypocholesterolemic acitivity of aliphatic compounds related to 2,8-dibenzylcyclooctanone. Journal of Medicinal Chemistry 18(10), 234-236.

4.5 Developmental Toxicity

CAS	821-55-6
Substance Name	2-Nonanone
Remarks for Substance	Data are for structurally related substance 2-heptanone, purity greater than 99%.
Method/guideline	OECD:TG- 421
Test Type	
GLP	Yes
Year	2001
Species/Strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of administration	Inhalation
Duration of test	Males were exposed for 50 days; females were exposed for 34-47 days (through day 19 of gestation)
Doses/concentration levels	0, 80, 400, or 1000 ppm. Actual exposure concentrations 0, 78.6, 405.8 or 1022.6 ppm
Exposure period	6 hours/day
Frequency of treatment	7 days/week
Control Group and treatment	Controls were exposed to filtered room air and housed similarly.
Remarks for test conditions	The ovaries, vagina, uterus, Fallopian tubes, and testes, epididymis, and male accessory sex organs were examined histologically. The testes and epididymis were also weighed. The study design also included an analysis of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.

NOAEL (NOEL) maternal toxicity	80 ppm
LOAEL (LOEL) maternal toxicity	400 ppm based on a reduction in activity
NOAEL (NOEL) developmental toxicity	1000 ppm
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	
Maternal data with dose level	All adult animals survived to study termination and there were no test substance-related changes in mean terminal body weight. For the 1000 ppm male group, there was a reduction in food consumption during days 0-7. Otherwise, there were no other differences in mean body weight, body weight gain, food consumption or food utilization among the groups throughout the study. Except for minimal reductions in activity level observed in the 400 and 1000 ppm groups during each exposure, no other test substance-related clinical abnormalities were noted. Mean sperm motility and mean epididymal spermatozoan and testicular spermatid counts were comparable among the groups. No test substance-related gross pathology was observed for adult animals from any group. No exposure-related changes were observed during histological examination of the reproductive organs of any of the test substance-exposed animals.
Fetal data with dose level	There were no treatment-related changes in pup clinical signs, weight gain, or abnormalities compared to controls at any of the test concentrations.
Appropriate statistical evaluations?	Homogeneity of data were evaluated by Bartlett's test (p,0.01), analysis of variance (ANOVA, less than 0.05), and Dunnett's test (p,0.05). When the variances of the means were not considered equal by Bartlett's test, the data were evaluated by Kruskal-Wallis H-test (p,0.05) followed by Mann-Whitney U-test ($p<0.05$). The reproductive performance of dams and fertility and fecundity indices were evaluated in contingency tables, using Chi-square test (p,0.05). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated by a linear regression model.
Remarks for results	
Conclusion remarks	Test material did not induce reproductive or developmental toxicity under the conditions of this assay at exposure levels up to 1000 ppm.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Eastman Kodak Co. (1996) Reproduction/Developmental toxicity screening test in the rat. Toxicological Sciences Laboratory, Health and Environment Laboratories. Study No. HAEL 95-0202.

CAS	112-12-9
Substance Name	2-Undecanone
Remarks for Substance	Data are for structurally related substance, 6,10-dimethyl-2-undecatrienone, purity greater than 98% by HPLC.
Method/guideline	Experimental/Retinoid Teratogenicity
Test Type	Developmental Toxicity
GLP	No
Year	1986
Species/Strain	Hamster/Golden Syrian
Sex	Female
Route of administration	Oral-Gavage
Duration of test	14 days (days 1 to 14 of pregnancy)
Doses/concentration levels	0, 96, or 960 mg/kg
Exposure period	days 1-14 of pregnancy
Frequency of treatment	Single high dose level on Day 8 of pregnancy
Control Group and treatment	Control group received Tween 20 (0.5 ml/100g)
Remarks for test conditions	Timed pregnant LAK:LVG(SYR) hamsters were given the test material dissolved in acetone and solubilized in polyoxyethylene sorbitan monolaurate. The test material was administered by gavage. Fetal and maternal body weights were monitored on Day 14. Full batteries of developmental parameters were monitored. Pregnant uteri were collected after laparatomy. The numbers of resorption and dead fetuses were recorded. Live fetuses were weighed and one-third of each litter was fixed in Bouin's fluid and subsequently sectioned in the mid-sagittal plane. Two-thirds of each litter were processed for skeletal examination. Abnormal litters were those containing one or more malformed fetuses or three or more resorbed implantation sites.
NOAEL (NOEL) maternal toxicity	96 mg/kg
LOAEL (LOEL) maternal toxicity	960 mg/kg
NOAEL (NOEL) developmental toxicity	960 mg/kg
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	

Maternal data with dose level	Maternal body weight was significantly depressed at 960 mg/kg. There were no significant changes in any other maternal parameter monitored.
Fetal data with dose level	There were no significant changes in any fetal parameter and no malformations were observed at either dose level.
Appropriate statistical evaluations?	Fetal and maternal body weight data analyzed by Neman-Keuls test, number of absorptions by Mann-Whitney test, and number of litters by Yates X2 test.
Remarks for results	There was no evidence of maternal toxicity at 96 mg/kg and no evidence of developmental toxicity at 960 mg/kg in golden Syrian hamsters.
Conclusion remarks	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Willhite C. C. (1986) Structure-activity relationships of retenoids in developmental toxicology. II Influence of polyene chain of the Vitamin A molecule. Toxicology and Applied pharmacology, 83, 563-575.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related ketone 3,5,5-trimethylcyclohexenone, assay 96.8%.
Method/guideline	
Test Type	Inhalation teratology study
GLP	No
Year	1984
Species/Strain	Rat/Sprague Dawley
Sex	Female
Route of administration	Inhalation
Duration of test	6 hrs/day for days 6 through 15 of gestation
Doses/concentration levels	0, 25, 50, or 115 ppm
Exposure period	Days 6 to 15 of pregnancy
Frequency of treatment	Daily
Control Group and treatment	Control group received conditioned air.
Remarks for test conditions	Groups of pregnant female Fischer F344 rats (22/group, 11 weeks old) were exposed to atmospheres containing 0, 25, 50, or 115 ppm of 3,5,5-trimethyl-2-cyclohexenone 6 hours daily

	from days 6 to 15 of pregnancy. Rats were weighted on days 0, 3, 6, 9, 12, 15, 18, or 20 of the study. Food consumption was measured for the same three day intervals. Dams were sacrificed on Day 20 and the intact uteri with ovaries were weighed. The uterus was examined for live and dead fetuses and late and early resorptions. The stained uterus of each animal was examined for implantation site and Corpora lutea were counted. Live and dead fetuses were weighed, examined for abnormalities, and crown rump distance was measured. One half the fetuses from each litter were decapitated and the heads were preserved, sectioned and examined (Wilson's technique). The viscera of all fetuses were processed, staine (Alizarin Red) and examined. Fetuses that have no been decapitated were examined for skeletal malformations and ossification variations. Late resorptions were weighed and examined grossly. Three animals of each sex were selected prior to the study and 6 females at conclusion of the study were selected. These animals were subjected to necropsy, gross examination, and viral blood examination. A wide variety of tissues were taken grossly examined.
NOAEL (NOEL) maternal toxicity	115 ppm
LOAEL (LOEL) maternal toxicity	
NOAEL (NOEL) developmental toxicity	115 ppm
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	
Maternal data with dose level	There were deaths during the study. Mean body weights of the high exposure group were depressed on days 12-15 compared to controls. This correlated with decreased food consumption during days 6 to 20. Clinical observations included a dose-related alopecia and cervical and ano-genital staining. There were no significant differences in mean uterine implantation and fetal evaluation data between test and control groups. At necropsy, there were no significant abnormalities reported in any treatment or control group animals.
Fetal data with dose level	The incidence of malformations (fusion of the malar and maxillary or processes of the jaw) were similar for test and control animals. No significant differences were reported in the mean body weights and mean crown-rump distances between test and control animals.
Appropriate statistical evaluations?	Bartlett's test for homogeneity of variance was used to determine if test and control groups showed equivalent variance at the 1% level of significance. If variances were significant a linear regression was performed. To test for dose response Duncan's test was perfomed. If variances were not equivalent, non-parameteric analysis was performed with a Kruskal-Wallis test.

Remarks for results	
Conclusion remarks	Under conditions of the test, dose levels of 0,25, 50, or 115 ppm of 3,5,5-trimethyl-2-cyclohexenone were not fetotoxic or teratogenic.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Traul K.A. (1984) Inhalation teratology study in mice and rats. Biodynamics Inc. Project No. 323772. Unpublished report.
CAS	2979-19-3
Substance Name	3,3-Dimethylcyclohexanone
Remarks for Substance	Data are for structurally related ketone 3,5,5-trimethylcyclohexenone, assay 96.8%
Method/guideline	
Test Type	Inhalation teratology study
GLP	No
Year	1984
Species/Strain	Mice/CD-1
Sex	Female
Route of administration	Inhalation
Duration of test	6 hrs/day for days 6 through 15 of gestation
Doses/concentration levels	0, 25, 50, or 115 ppm
Exposure period	Days 6 to 15 of pregnancy
Frequency of treatment	Daily
Control Group and treatment	Control group received conditioned air.
Remarks for test conditions	Groups of pregnant female CD-1 mice (22/group, 9 weeks old) were exposed to atmospheres containing 0, 25, 50, or 115 ppm of 3,5,5-trimethyl-2-cyclohexenone 6 hours daily from days 6 to 15 of pregnancy. Mice were weighted on days 0, 3, 6, 9, 12, 15, and 18, of the study. Food consumption was measured for the same three day intervals. Dams were sacrificed on Day 18 and the intact uteri with ovaries were weighed. The uterus was examined for live and dead fetuses and late and early resorptions. The stained uterus of each animal was examined for implantation site and Corpora lutea were counted. Live and dead fetuses were weighed, examined for abnormalities, and crown rump distance was measured. One half the fetuses from each litter were decapitated and the heads were preserved, sectioned and examined (Wilson's technique). The viscera of all

	fetuses were processed, staine (Alizarin Red) and examined. Fetuses that have no been decapitated were examined for skeletal malformations and ossification variations. Late resorptions were weighed and examined grossly. Three animals of each sex were selected prior to the study and 6 females at conclusion of the study were selected. These animals were subjected to necropsy, gross examination, and viral blood examination. A wide variety of tissues were taken grossly examined.
NOAEL (NOEL) maternal toxicity	115 ppm
LOAEL (LOEL) maternal toxicity	
NOAEL (NOEL) developmental toxicity	115 ppm
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	
Maternal data with dose level	There were deaths during the study. Mean body weights of the high exposure group were depressed compared to controls. There were no significant differences in mean uterine implantation and fetal evaluation data between test and control groups. At necropsy there was no significant abnormalities reported in any treatment or control group animals.
Fetal data with dose level	The predominant skeletal malformation was an extra area of ossification between the frontal bones of the head. However, there were no significant differences between test and control groups. There were no significant differences in the mean body weights and mean crown-rump distances between test and control animals.
Appropriate statistical evaluations?	Bartlett's test for homogeneity of variance was used to determine if test and control groups showed equivalent variance at the 1% level of significance. If variances were significant a linear regression was performed. To test for dose response Duncan's test was perfomed. If variances were not equivalent, non-parameteric analysis was performed with a Kruskal-Wallis test.
Remarks for results	
Conclusion remarks	Under conditions of the test, dose levels of 0, 25, 50, or 115 ppm of 3,5,5-trimethyl-2-cyclohexenone were not fetotoxic or teratogenic.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Traul K.A. (1984) Inhalation teratology study in mice and rats. Biodynamics Inc. Project No. 323772. Unpublished report.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Based on inconvertibility of alcohol and ketones in vivo, data for structurally related alcohols 2-Isopropyl-5-methylcyclohexanol are presented.
Method/guideline	
Test Type	Teratology study
GLP	Pre-GLP
Year	1973
Species/Strain	Mouse/CD-1 outbred
Sex	Female
Route of administration	Gavage
Duration of test	10 days
Doses/concentration levels	0(negative control), 0, 1.85, 8.59, 39.9, 185 mg/kg bw/day and a positive control of 150 mg/kg bw/day of aspirin.
Exposure period	Days 6 to 15 of gestation
Frequency of treatment	Daily
Control Group and treatment	Control group received corn oil vehicle (10 ml//kg); Positive control received 150 mg/kg bw/day of aspirin in corn oil
Remarks for test conditions	Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female CD-1 outbred mice were gang-housed in plastic disposable cages in a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. There were mated with untreated young adult males and observation of vaginal sperm plugs was considered day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, groups (22-23/group) of pregnant females were given 0, 1.85, 8.59, 39.9, 185 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 150 mg/kg bw/day of aspirin. Body weights were recorded on days 0, 6, 11, 15, and 17 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 17 all dams were subjected to Caesarean section and the number of implantation sites, number of resorptions, % of live and % partial live resorptions, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. One-third of fetuses of each litter underwent detailed visceral examination at 10x magnification. The remaining two-thirds were stained with alizarin red S dye/KOH and examined for

	skeletal defects.
NOAEL (NOEL) maternal toxicity	185 mg/kg bw/day
LOAEL (LOEL) maternal toxicity	
NOAEL (NOEL) developmental toxicity	185 mg/kg bw/day
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	0, 1.85, 8.59, 39.9, 185 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Daily clinical observation and measurement of body weight gain failed to show any differences between control and test groups of female mice. The number pregnant and % pregnancy were similar for all dose and control groups. No abortions were observed in any group. The number of live litters, average implant sites per dam were similar for both test and control groups. The % partial resorptions and % complete resorption were increased for the 1.85 and 8.59 mg/kg bw groups, but higher dose levels exhibited lower resorption rates compared to the control groups.
Fetal data with dose level	The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and control groups. Also, there was no significant difference in the number of dead fetuses between test and control groups. Skeletal examination of sternebrae showed no significant differences in the incidence of incomplete ossification or missing sternebrae for test and negative control groups. There was evidence of incomplete ossification in the positive control group. Likewise the incidences of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure were similar for test and negative control animals. Visceral examination failed to reveal any evidence of soft tissue abnormalities at any dose level.
Appropriate statistical evaluations?	
Remarks for results	
Conclusion remarks	There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 185 mg/kg bw/day of test material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Morgareidge K. (1973a) Teratologic evaluation of FDA 71-57 in mice. Contract No. FDA 71-260. Unpublished report.
CAS	2816-57-1

Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Based on inconvertibility of alcohol and ketones in vivo, data for structurally related alcohols 2-Isopropyl-5-methylcyclohexanol are presented.
Method/guideline	
Test Type	Teratology study
GLP	Pre-GLP
Year	1973
Species/Strain	Rat/female Wistar
Sex	Female
Route of administration	Gavage
Duration of test	10 days
Doses/concentration levels	0(control), 2.18, 10.15, 47.05, 218 mg/kg bw/day and a positive control of 250 mg/kg bw/day of aspirin in corn oil.
Exposure period	Days 6 to 15 of gestation
Frequency of treatment	Daily
Control Group and treatment	Control group received corn oil vehicle (10 ml//kg); Positive control received 250 mg/kg bw/day of aspirin in corn oil
Remarks for test conditions	Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female rats were individually housed in mess bottom cages in a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. There were mated with untreated young adult males and observation of vaginal sperm plugs was considered day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, groups (22-25/group) of pregnant females were given 0, 2.18, 10.15, 47.05, 218 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 250 mg/kg bw/day of aspirin. Body weights were recorded on days 0, 6, 11, 15, and 20 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 20 all dams were subjected to Caesarean section and the number of implantation sites, number of resorptions, % of live and % partial live resorptions, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. One-third of fetuses of each litter underwent detailed visceral examination at 10x magnification. The remaining two-thirds were stained with alizarin red S dye/KOH and examined for skeletal defects.

NOAEL (NOEL) maternal toxicity	218 mg/kg bw/day
LOAEL (LOEL) maternal toxicity	
NOAEL (NOEL) developmental toxicity	218 mg/kg bw/day
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	0, 2.18, 10.15, 47.05, 218 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Daily clinical observation and measurement of body weight gain failed to show any differences between control and test groups of female rats. The number pregnant and % pregnancy were similar for all dose and control groups. No abortions were observed in any group. The number of live litters, average implant sites per dam were similar for both test and control groups. The % partial resorptions and % complete resorption were increased only for the positive control group.
Fetal data with dose level	The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and negative control groups. Also, there no dead fetuses in either the test or negative control groups. The positive control group did show dead fetuses (3) and dams with more than one dead fetus. The positive control group also exhibited a decreased number of live fetuses and decreased average fetal weight compared to those for the negative control. Skeletal examination of sternebrae, vertebrae, skull, ribs, extremities, and soft tissues showed no significant differences between test and negative control groups. The positive control group showed a significant increase in incidence of missing sternebrae. Likewise, the positive control exhibited an increase in the incidence of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure. Visceral examination failed to reveal any evidence of abnormalities in either negative control or test groups. In the positive control group, meningoencephalocele and spina bifida were reported.
Appropriate statistical evaluations?	
Remarks for results	
Conclusion remarks	There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 218 mg/kg bw/day of test material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Morgareidge K. (1973b) Teratologic evaluation of FDA 71-57 in rats. Contract No. FDA 71-260. Unpublished report.

CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone
Remarks for Substance	Based on inconvertibility of alcohol and ketones in vivo, data for structurally related alcohols 2-Isopropyl-5-methylcyclohexanol are presented.
Method/guideline	
Test Type	Teratology study
GLP	Pre-GLP
Year	1973
Species/Strain	Hamster/female golden
Sex	Female
Route of administration	Gavage
Duration of test	5 days
Doses/concentration levels	0(control), 4.05, 21.15, 98.2, or 405 mg/kg bw/day and a positive control of 250 mg/kg bw/day of aspirin
Exposure period	Days 6 to 10 of gestation
Frequency of treatment	Daily
Control Group and treatment	Control group received corn oil vehicle (10 ml//kg); Positive control received 250 mg/kg bw/day of aspirin in corn oil
Remarks for test conditions	Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female hamsters were individually housed in mess bottom cages in a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. There were mated one to one with untreated young adult males and the appearance of motile sperm in the vaginal sperm was considered day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, groups (19-23/group) of pregnant females were given 0, 64.05, 21.15, 98.2, or 405 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 250 mg/kg bw/day of aspirin. Body weights were recorded on days 0, 8, 10, and 14 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 14 all dams were subjected to Caesarean section and the number of implantation sites, resorption sites, % of live and % partial live resorptions, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. One-third of fetuses of each litter underwent detailed visceral examination at 10x magnification. The remaining two-thirds were stained with alizarin red S dye/KOH

	and examined for skeletal defects.
NOAEL (NOEL) maternal toxicity	405 mg/kg bw/day
LOAEL (LOEL) maternal toxicity	
NOAEL (NOEL) developmental toxicity	405 mg/kg bw/day
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	0, 4.05, 21.15, 98.2, or 405 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Daily clinical observation and measurement of body weight gain failed to show any differences between control and test groups of female rats. The number pregnant and % pregnancy were similar for all dose and control groups. No abortions were observed in any group.
Fetal data with dose level	The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and control groups. There was one dead fetus in the negative control and the 4.05 and 21.15 dose groups, but none in the higher dose groups. There were 18 dead fetuses in the positive control group. Skeletal examination of sternebrae showed no significant differences in the incidence of incomplete ossification or missing sternebrae for test and control groups. Likewise the incidences of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure were similar for test and control animals. An increased incidence of incomplete ossification of the vertebrae was reported in the two mid-dose groups but not in the highest (405 mg/kg bw) group. Visceral examination of tissues failed to reveal any evidence of significant abnormalities at any dose level.
Appropriate statistical evaluations?	
Remarks for results	
Conclusion remarks	There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 405 mg/kg bw/day of test material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Morgareidge K. (1973c) Teratologic evaluation of FDA 71-57 in hamsters. Contract No. FDA 71-260. Unpublished report.
CAS	2816-57-1
Substance Name	2,6-Dimethylcyclohexanone

Remarks for Substance	Based on inconvertibility of alcohol and ketones in vivo, data for structurally related alcohols 2-Isopropyl-5-methylcyclohexanol are presented.
Method/guideline	
Test Type	Teratology study
GLP	Pre-GLP
Year	1973
Species/Strain	Rabbit/virgin, adult, Dutch belted
Sex	Female
Route of administration	Gavage
Duration of test	13 days
Doses/concentration levels	0(control), 4.25, 19.75, 91.7, 425 mg/kg bw/day and a positive control of 250 mg/kg bw/day of aspirin in corn oil.
Exposure period	Days 6 to 18 of gestation
Frequency of treatment	Daily
Control Group and treatment	Control group received corn oil vehicle (10 ml//kg); Positive control received 2.5 mg/kg bw/day of 6-aminonictineamide in corn oil on Day 9
Remarks for test conditions	Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female rabbits were individually housed in mess bottom cages in a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. On day 0, does were given an injection of 0.4 l of human chorionic gonadotropin (400 IU). Three hours later, each doe was artificially inseminated with 0.3 ml of semen from a buck using approximately 20 x 10e6 motile sperm. Beginning on Day 6 and continuing daily through Day 18 of gestation, groups (11-14/group) pregnant females were given 0, 4.25, 19.75, 91.7, 425 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 2.5 mg/kg bw/day of 6-aminonicotinamide. Body weights were recorded on days 0, 6, 8, 12, 18, and 29 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 29 all dams were subjected to Caesarean section and the number of corpora lutea, implantation sites, resorption sites, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. All live fetuses were placed in an incubator for 24 hours and evaluated for survival. All surviving pups were sacrificed and subjected to detailed visceral examination at 10x magnification. All fetuses were cleared with KOH, stained with

	alizarin red S dye, and examined for skeletal defects.
NOAEL (NOEL) maternal toxicity	425 mg/kg bw/day
LOAEL (LOEL) maternal toxicity	
NOAEL (NOEL) developmental toxicity	425 mg/kg bw/day
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	0, 4.25, 19.75, 91.7, 425 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Survival of dams at term was similar for test, positive and negative control groups. Daily clinical observation and measurement of body weight gain failed to show any differences between control and test groups of female rabbits. The number pregnant and % pregnancy were similar for all dose and control groups. One to four pregnant female died in both control groups and in the four test groups. There was no dose response relationship for mortality in the test groups. There was no statistical difference in the number of live litters, corpora lutea, implantation sites, or resorption sites between the negative control group and any test group.
Fetal data with dose level	The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and control groups. Also, there was no significant difference in the number of dead fetuses between test and control groups. Except for positive control group, skeletal examination of sternebrae and vertebrae showed no significant differences in the incidence of incomplete ossification or missing sternebrae for test and untreated control group. Likewise the incidences of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure were similar for test and the untreated control group The positive 6-aminonicotinaminde-treated control group showed increases in incidence of fused and split ribs. Visceral examination failed to reveal any evidence of abnormalities in either negative control or test groups. In the positive control group, medial rotation of the hind limb and anopia were reported in pups from 7 of the 11 litters.
Appropriate statistical evaluations?	
Remarks for results	
Conclusion remarks	There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 425 mg/kg bw/day of test material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.

References	Morgareidge K. (1973d) Teratologic evaluation of FDA 71-57 in rabbits. Contract No. FDA 71-260. Unpublished report.
CAS	928-68-7
Substance Name	6-Methyl-2-heptanone
Remarks for Substance	Data are for structurally related substance 5-methyl-2-hexanone purity greater than 99%.
Method/guideline	OECD:TG- 421
Test Type	
GLP	Yes
Year	2001
Species/Strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of administration	Inhalation
Duration of test	Males were exposed for 51 days; females were exposed for 35-41 days (through day 19 of gestation).
Doses/concentration levels	0, 1, 2.5, 5 mg/L. Actual exposure 0.965, 2.32, and 4.72 mg/L
Exposure period	6 hours/day
Frequency of treatment	7 days/week
Control Group and treatment	Controls were exposed to filtered room air and housed similarly.
Remarks for test conditions	The study design also included an analysis of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
NOAEL (NOEL) maternal toxicity	5 mg/L
LOAEL (LOEL) maternal toxicity	
NOAEL (NOEL) developmental toxicity	5 mg/L
LOAEL (LOEL) developmental toxicity	
Actual dose received by dose level and sex	
Maternal data with dose level	All adult animals survived to study termination and there were no test substance-related changes in mean terminal body weight. For the 5 mg/L male group, the mean body weight gain and mean food utilization were higher (p 0.05) on Day 35 when compared with the control group. Otherwise, there were no other differences in mean body weight, body weight gain, food consumption or food utilization among the groups throughout

	the study. Except for minimal reductions in activity level observed in the 5 mg/L group during each exposure, no other test substance-related clinical abnormalities were noted. Mean sperm motility and mean epididymal spermatozoan and testicular spermatid counts were comparable among the groups. No test substance-related gross pathology was observed for adult animals from any group. No exposure-related changes were observed during histological examination of the reproductive organs of any of the test substance-exposed animals.
Fetal data with dose level	Although trend analyses indicated reductions in the total number of pups per litter and in the number of live pups per litter. The Kruskal-Wallis H-test indicated that the total number of pups per litter and the number of live pups per litter were comparable among the groups. Abnormalities were observed for occasional pups from the 5.0, 2.5, and 0.0 mg/L groups. These abnormalities included the pups appearing small, having no milk in their stomachs, and having bruises under the skin. Additionally, pups were occasionally missing (presumable cannibalized) or found dead. Since the clinical abnormalities were observed for comparable numbers of pups from the control and treated groups and since the number of dead pups was not statistically different among the groups, these findings were not considered to be test substance-related.
Appropriate statistical evaluations?	
Remarks for results	
Conclusion remarks	Test material did not induce reproductive or developmental toxicity under the conditions of this assay at exposure levels up to 5 mg/L.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Eastman Kodak Co. (2001b) Reproduction/Developmental toxicity screening test in the rat. Toxicological Sciences Laboratory, Health and Environment Laboratories. Study No. HAEL 2000-0208. Laboratory Project ID 200020 8I1.